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OVERSIGHT HEARING ON IMPLEMENTATION OF NIH GUIDELINES GOVERNING RECOMBINANT DNA RESEARCH

JOINT HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

U.S. Congress. Senate

COMMITTEE ON
LABOR AND PUBLIC WELFARE

AND THE

SUBCOMMITTEE ON
ADMINISTRATIVE PRACTICE AND PROCEDURE

OF THE

COMMITTEE ON THE JUDICIARY
UNITED STATES SENATE

NINETY-FOURTH CONGRESS

SECOND SESSION

ON

EXAMINATION OF NIH GUIDELINES GOVERNING
RECOMBINANT DNA RESEARCH

SEPTEMBER 22, 1976

Printed for the use of the Committee on Labor and Public Welfare
and the Committee on the Judiciary

U.S. GOVERNMENT PRINTING OFFICE
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OVERSIGHT HEARING ON IMPLEMENTATION OF NIH GUIDELINES GOVERNING RECOMBINANT DNA RESEARCH

WEDNESDAY, SEPTEMBER 22, 1976

U.S. Senate,
Subcommitee on Health of the
Committee on Labor and Public Welfare,
Subcommittee on Administrative Practice
and Procedure of the Committee on the Judiciary,
Washington, D.C.

The subcommittees met, pursuant to notice, at 9:34 a.m., in room 4232 Dirksen Senate Office Building, Senator Edward M. Kennedy (chairman of the subcommittees) presiding.

Present: Senators Kennedy, Javits, and Schweiker.

Committee staff present: Stanley Jones, professional staff member, and Jay Cutler, minority counsel.

Senator Kennedy. The subcommittees will come to order.

This morning the Senate Health Subcommittee and Administrative Practice and Procedure Subcommittee returns to the subject of genetic engineering. No area of scientific inquiry has generated the degree of public controversy which currently surrounds those scientists who have learned to create new forms of life in the laboratory.

I believe that the vigorous public debate over the potential benefits and risks of this work is much to the good. An important precedent is being set. It is that the implications of technological advances must be carefully considered early on, and must be considered in public processes with wide participation from as many diverse elements of society as possible.

Recombinant DNA research presents a prototype of the problems our society will face over and over again as technology develops. The issues go far beyond safety questions—in many ways, those are the easiest to answer. The real problem is to understand the social consequences of what science can now enable us to do.

As long as the development of technology outstrips man's capacity to understand the implications of that technology, the chances for serious errors in judgment are increased and the possibility for serious societal disruption is very real.

Thus, I believe the debate over genetic engineering must go on. Scientists must tell us what they are capable of doing, but we as members of society must decide how it should be or whether it should be applied. Congress cannot legislate an appropriate answer in this matter. But it can and should take the lead in assuring that these issues are discussed publicly, and by as broad a segment of the population as possible.

The plain fact is that genetic engineering has the capacity to change our society. How do we want it changed? What uses can we make of this knowledge? What degree of change is desirable, and at what rate? What kind of society do we want to become? These are the questions that must be answered and the development of those answers must involve as many Americans as possible.

While these discussions take place, however, and while the research continues, we face the immediate, practical problem of assuring that the research is as safe as possible with the fewest risks to the fewest people.

Today we will focus on the guidelines that the National Institutes of Health have developed for recombinant DNA research. Although not perfect, the guidelines are generally considered to be an important step in the reduction of risk in this area. The problem is that many groups doing research do not fall under these guidelines.

It is my belief that, at the very least, all Federal agencies should comply with the NIH guidelines. These guidelines need not be viewed as fixed or final. But they should be observed while appropriate modifications are made. I also believe that industry research in this area should conform to NIH guidelines.

The potential for industrial abuse is present in part because of the tradition of secrecy which surrounds potentially profitable research. There are ways to protect legitimate trade secret information and still have Federal monitoring of DNA research in industry NIH.

I would hope that industry would voluntarily comply with the guidelines. If they do not, we will have to consider legislative action.

My concerns over industry compliance have been raised bv the refusal of the General Electric Co. to testify at this hearing. Their excuse was that their top scientist in this area is unavailable. They refused to send a corporate official to discuss General Electric's overall policy in this area. We wanted to know what research they are doing, and they contemplate, and whether they can comply with the NIH guidelines.

This subcommittee is grateful for the cooperation of the Pharmaceutical Manufacturers Association in this hearing. But the actions of GE make it clear that we will have to have a complete accounting of all industrial research and development in this area. I have directed the subcommittee staff to vigorously pursue the matter as a high priority activity.

I might just mention at the conclusion of these brief opening remarks of the enormous amount of interest that this whole issue has in the important research area of Cambridge in my own State of Massachusetts. This has brought great interest within the local community, and part of the NIH guidelines were to include the component to include the public and local community involvement in this decision-making process, the location of this research.

I think there has been a responsible attitude shown by community officials. They do want knowledge. They do want to understand more completely the nature of the risk.

In my meetings with some of those officials I pointed out that perhaps people in those particular areas, perhaps in Cambridge or in

Greater Boston area, may very well be under greater risk from research being done not in that particular sector, which are attempting to follow the NIH guidelines, but research being done in other industries or in other centers that are not following the NIH guidelines.

It is extremely important, I think, for the benefit of the American people to really ventilate this issue and question. Obviously we want to see the progress of knowledge and technology in ways that can help move our society, and in useful and important ways.

We are very much aware that the potential benefits are virtually unlimited, and the potential risks appear to be, as well.

Obviously, we hope as a result of these hearings to inform ourselves and inform the Congress, and inform the American people as to what public policy questions ought to be raised, and how we as an institution can best help respond in a responsible manner.

I will make a part of the record the letter Senator Javits and I sent to the President urging that the application of these various guidelines be applicable to all Federal agencies we have not received a response to.

The fact is, as we know, we are really talking about the stroke of a pen in terms of any kind of Executive order of that description.

There is an interagency task force that has been meeting and working for probably far too long without some action in this area. We want to listen to two witnesses this morning who can speak about those particular issues, Donald Fredrickson of NIH, and Wilson Talley is the Assistant Administrator for the Research and Development of the EPA.

Before they testify, I want to recognize my colleagues, Senator Javits, who has worked very closely with us in this whole area.

Senator Javits. Mr. Chairman, I have worked very closely with you. I will continue to work very closely with you. It is a matter of the most constant interest and admiration to me the amount of time that you devote to this particular subcommittee. It is an extraordinary concentration and effort of very high order on your part on behalf of all Americans.

I am very glad you follow it as closely as you do.

As ranking member of the whole committee, I am very pleased to have our ranking member on the Health Subcommittee, Senator Schweiker of Pennsylvania, work with you, very cooperatively.

I will do my utmost to continue to see that the minority plays its proper part.

On the merits of what you have just mentioned, I think that the letter to the President requires and deserves an answer. I will do my best to get it from him promptly, so it may be part of these hearings.

Second, as to the danger which is involved to the public, I would like to offer for the record a New York Times Sunday magazine piece, August 22, by a researcher of long experience, Liebe F. Cavalieri, on this very subject which the chairman has referred to.

I ask unanimous consent that it may be made a part of my remarks.

Senator Kennedy. Without objections, so ordered.

[The letter and material referred to follows:]

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United States Senate

COMMITTEE ON
LABOR AND PUBLIC WELFARE
WASHINGTON, D.C. 20510

July 19, 1976

The President
The White House
Washington, D.C.

Dear Mr. President:

For several years, the biomedical research community has been engaged in an extremely important debate over the safety of certain types of genetic research. The research involves combining genetic material from different organisms. The technology that permits this type of genetic experimentation, called recombinant DNA research, is revolutionary; and holds the promise of enormous benefits in our understanding of disease processes, and could lead us to ways of controlling or treating complex diseases such as cancer and hereditary defects. It could conceivably lead to improved ways of producing such important hormones as insulin, clotting factors, and enzymes important to treatment of many diseases. The technology also has conceivable applications in agriculture and industry. Clearly, it is a research area of enormous promise.

However, recombinant DNA research also entails unknown but potentially enormous risks due to the possibility that microorganisms with transplanted genes might prove hazardous to human and other forms of life--and might escape from the laboratory. Indeed, scientists engaged in such research declared a voluntary moratorium on recombinant DNA research in 1974 when they foresaw the possibility, for example, of creating in the laboratory self-propagating infectious bacteria that contain genes from cancer-causing viruses. The moratorium was lifted in 1975, but maintained, again by the researchers themselves, for the specific types of experiment which might produce cancer-causing bacteria, raise the resistance of antibiotics of known bacteria, or have other dangerous results.

On June 23rd of this year, the National Institutes of Health issued comprehensive guidelines for recombinant DNA research which specify more stringent safety and containment measures than are currently required or practiced in many areas. They specifically prohibit the most potentially dangerous types of experiments. In addition, the guidelines prohibit the release into the air or water or environment of any of the genetic materials created by the research.

We appreciate the great care NIH has taken, in the formulation of these strict guidelines, in obtaining the best scientific advice as well as advice from experts in law and ethics. Opportunity was also given for the public to comment on the guidelines. The environmental impact assessment of the guidelines currently being prepared by NIH will offer further opportunities for such comment.

The guidelines will be widely discussed and debated with regard to their ultimate adequacy in safeguarding the public, and they will no doubt further evolve and develop during this debate and as our understanding of recombinant DNA advances. Based on the process by which NIH produced the present guidelines, we are confident they are a responsible and major step forward and reflect a sense of social responsibility on the part of the research community and the NIH.

However, we are gravely concerned that these relatively stringent guidelines may not be implemented in all sectors of the domestic and international research communities and that the public will therefore be subjected to undue risks. The National Institutes of Health has the authority to require adherence to the guidelines as a condition of their grants and contracts for research, but they cannot enforce the guidelines with respect to other Federal agencies, with respect to research in the private sector in this country, and with respect to research done in other nations.

In particular, it is clear that recombinant DNA research has great potential in the private sector, such as pharmaceutical manufacture, the oil industry and agricultural products. It is also clear that some elements of the guidelines, such as limitations on the size of experiments, public disclosure, and non-release of materials into the environment, may be contrary to the interest and practice of research in private industry, and may therefore be ignored. In addition, since private sector research will lead to industrial application, guidelines must be extended beyond research into application and production stages. If the NIH guidelines are necessary to protect the public in Federally funded research, it is clear they are necessary for privately funded research and application as well.

Given the high potential risks of this research, it seems imperative that every possible measure be explored for assuring that the NIH guidelines are adhered to in all sectors of the research community. We urge you to implement these guidelines immediately wherever possible by executive directive and/or rulemaking, and to explore every possible mechanism to assure compliance with the guidelines in all sectors of the research community, including the private sector and the international community. If legislation is required to these ends, we urge you to expedite proposals to Congress.

This is an unprecedented issue in the area of biomedical research. It has been likened in importance to the discovery of nuclear fission. In the interest of public safety, and in the interest of permitting this beneficial research to continue with the blessing of a reassured public, we must act expeditiously on these matters.

Sincerely,

Jacob K. Javits
Ranking Minority Member
Committee on Labor and
Public Welfare

Edward M. Kennedy
Chairman
Subcommittee on Health

THE WHITE HOUSE
WASHINGTON

September 22, 1976

Dear Mr. Chairman:

I am writing in response to your and Senator Javits' letter of July 19 concerning the National Institutes of Health (NIH) Guidelines on Recombinant Deoxyribonucleic Acid (DNA) Research. As you note in your letter, the Guidelines were developed over an 18-month period and involved the participation not only of the scientific community but of the public as well.

I am advised by the Secretary of Health, Education, and Welfare that the potential scientific and medical benefits in this research area are promising and that support for the research is merited with appropriate safeguards against possible hazards. The material accompanying the release of the Guidelines explained in great detail the care and consideration given stated public concerns for safety.

The application of these Guidelines beyond the NIH to the public and private sectors merits further consideration. To consider this and other issues further Secretary Mathews has proposed that an inter-agency committee be created to review the activities of all Government agencies conducting or supporting recombinant DNA research or having regulatory authority relevant to this scientific field. The committee could also coordinate activities with non-Federal institutions. I have written to all Department Secretaries urging their cooperation and participation in naming representatives to serve on this proposed committee.

By this means I believe the concerns you address in your letter will receive careful attention. I am asking Secretary Mathews to keep you apprised of the deliberations of this committee and any recommendations that may be forthcoming.

Thank you very much for your thoughtful letter.

Sincerely yours,

Gerald R. Ford

The Honorable Edward M. Kennedy
Chairman, Subcommittee on Health
Committee on Labor and Public Welfare
United States Senate
Washington, D.C. 20510

[From the New York Times Magazine, August 22, 1976]

New strains of life—or death

Scientists have learned to rearrange the basic genetic material of living things, and so have opened an exciting new research frontier. But, one biologist warns, 'the future will curse us for it.'

By Liebe F. Cavalieri

Early in July, the 10-man City Council of Cambridge, Mass., at the urging of some concerned Harvard scientists, voted to ask Harvard University to halt temporarily the construction of a new $500,000 laboratory for specialized genetics research. This move on the part of the Mayor and other local elected officials against the scientific decisions of the university was unprecedented, but so was the dramatic reason for it—the fear that the biologists, who propose to tamper with the genetic apparatus of microorganisms, would create a new Andromeda-like strain that might escape their control and spread an incurable disease to the population.

The Cambridge Council's intervention in Harvard affairs cannot be dismissed as an overreaction of ignorant laymen to the esoteric pursuits of science, for it has been spurred by the carefully considered opinions of some distinguished workers in biological research—Nobelist George Wald is one of the leaders. They are concerned with the recently attained power of biology to alter the genes of living things and create new and possibly dangerous hybrids of animals, plants and viruses. Of course such alarms have been raised before: The A-bomb, nerve gas, biological warfare, the destruction of the stratospheric ozone layer by fluorocarbon sprays—all have been held up as threats to human existence. But all of these dangers can, in theory if not in practice, be limited or controlled. The threat of a new form of life is more compelling, for once released, it cannot be controlled, and its effects cannot be reversed. A new disease may simply have to run its course, attacking millions in its path. The Cambridge Council undoubtedly had some stark vision of such a biological holocaust when it made its decision. (Harvard responded to the council's request by setting up a committee to consider the city's concern about the laboratory.)

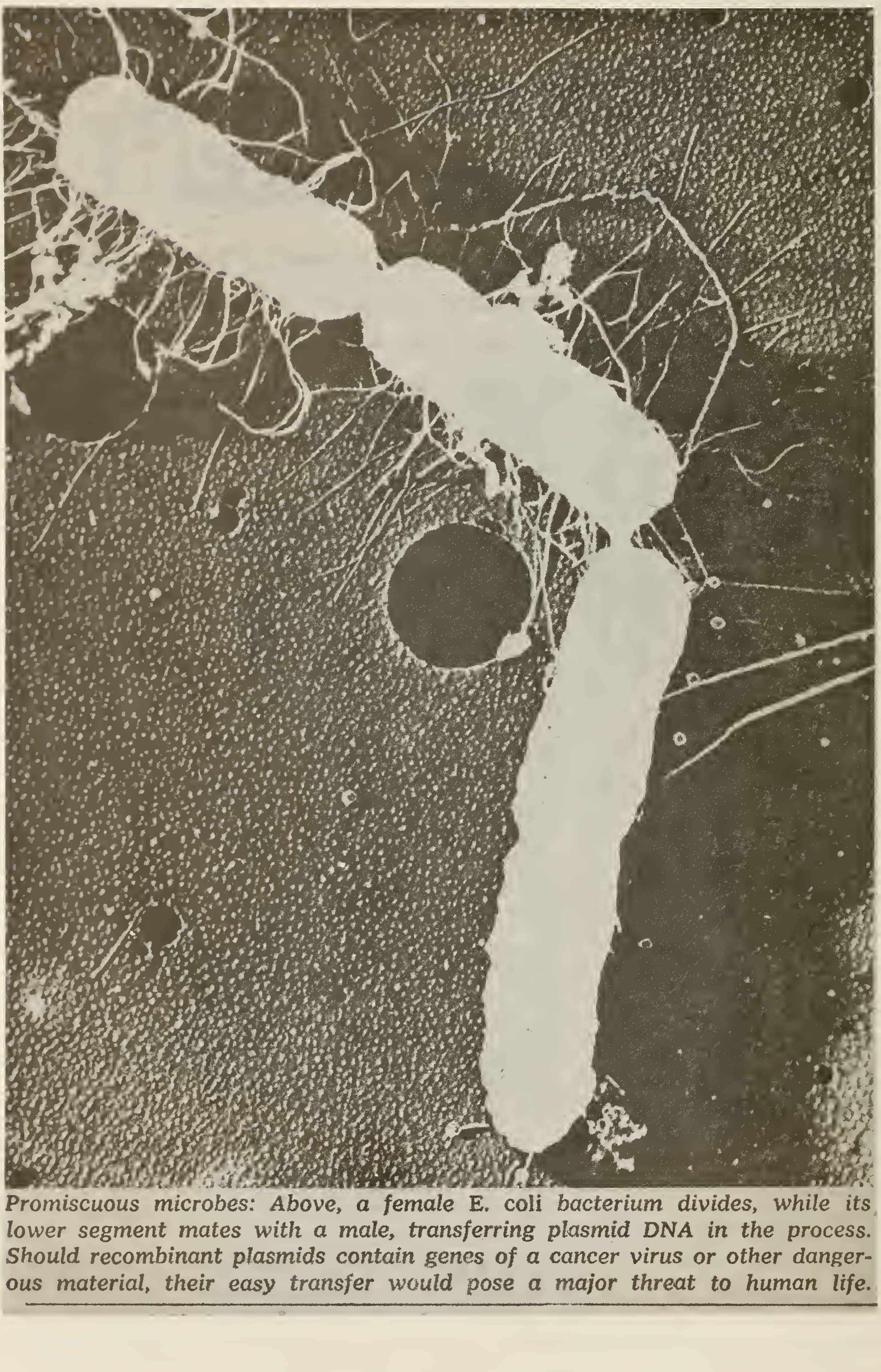
The scientists who alerted the Cambridge City Council are not typical. Most of those not directly involved in the new genetic research take a hands-off position, perhaps out of reluctance to interfere with the venerated "right" of scientists to free inquiry. They may also fear that negative publicity associated with biological research will disillusion the public and diminish the funds so necessary for all types of research. Meanwhile, scientists working in the controversial areas are motivated by their own intellectual curiosity and the powerful drive for success and recognition.

Recent discoveries in molecular genetics have provided spectacular new techniques whose exploitation is difficult to resist so long as scientists continue to focus on innovation rather than social benefit. The involved scientists are aware that their experimentation entails some risks to the public, but they argue that adequate precautions can be taken to make the risks acceptably small. For several years they have debated the risks and the steps that must be taken to minimize them. At a major international conference held early last year at the Asilomar conference center in Pacific Grove, Calif., leading molecular biologists took the rare step of proposing rules to limit genetic research. More recently, they have been instrumental in drawing up a similar set of guidelines that has just been issued by the Director of the National Institutes of Health.

The guidelines may alleviate the nervousness of some scientists, but—as a researcher in molecular biology for 25 years—my own view is that they will not effectively reduce the danger. Indeed, they may actually lull us into a false sense of security.

The danger has developed with the discovery of a special form of DNA, the substance that controls the growth and reproduction of all living cells. Ordinary DNA is a large molecule shaped like a double helix, or spiral staircase; it is found in the nucleus of every living cell. We now know that the arrangement of atoms in the helix reflects the code, or set of instructions, that guides the development of every cell in the fulfillment of its genetic destiny. The new form of DNA, known as recombinant DNA, is simply a mosaic of DNA fragments obtained from different types of cells. These patchwork molecules, man-made in the laboratory, have the power to enter a host cell and become a part of its permanent genetic complement. What they may do to the cell we do not know.

The discovery of recombinant DNA is one of the more striking technological achievements of our century. The story began in 1944 when a team of scientists, Oswald T. Avery, Colin MacCloud and Maclyn McCarty, at the



Promiscuous microbes: Above, a female E. coli *bacterium divides, while its lower segment mates with a male, transferring plasmid DNA in the process. Should recombinant plasmids contain genes of a cancer virus or other dangerous material, their easy transfer would pose a major threat to human life.*

Rockefeller Institute (now Rockefeller University) showed for the first time that DNA is the hereditary substance of living cells. Later work showed that the long DNA molecule is composed of sections called genes. Each gene determines a characteristic—hair color, for example. Another discovery important to the development of recombinant DNA was made by William Hayes and Joshua Lederberg in 1952. They showed that bacterial cells contain circular DNA molecules, called plasmids, in addition to the main DNA molecule. The plasmids are small, easy to handle in the laboratory and can enter other bacteria with ease. The plasmids also contain a series of genes, linked together in the form of a circle. In 1962, W. Arber and D. Dussoix showed that bacterial cells contain a substance, called a restriction enzyme, that acts as a fine chemical scalpel to split foreign DNA molecules into specific fragments. This process, part of the bacteria's defense mechanism, occurs when a bacterial virus infects a bacterium. The enzyme was purified from bacteria by H. Boyer and his co-workers, and in 1972 it was shown by J. Mertz and R. Davis of Stanford University School of Medicine that the split DNA fragments have "sticky ends"—when the ends touch they stick to each other. This astonishing characteristic of the DNA fragments makes genetic engineering possible.

Recombinant DNA is actually very easy to make. Any high school student can do it. Restriction enzymes are available commercially and may be used to split DNA molecules from any source—man, cancer viruses, bacteria, plants, insects—to produce fragments with sticky ends. When a split plasmid DNA from a harmless bacterium is mixed with another split DNA, say from a cancer virus, their sticky ends join, and a new, hybrid plasmid is formed. This new form of DNA has the characteristics of both DNA's—bacterial and cancer—from which it was made. To make vast quantities of this new entity, it is only necessary to mix the new plasmid DNA's with bacteria. The bacteria absorb them and then manufacture exact copies in limitless number. Using bacteria as factories in this way, any kind of recombinant DNA can be made in large quantity. This possibility is so attractive that both Stanford University and the University of California have applied for patents for DNA recombinant technology.

This technology is, of course, very exciting to molecular biologists. Its application to basic research promises to provide answers to a number of fundamental biological questions. With this desirable end result in mind, scientists feel justified in taking the risks inherent in the technique.

For example, Paul Berg, who directs a large facility at Stanford University School of Medicine, has stated that the ability to produce large quantities of gene fragments with recombinant DNA procedures permits expanded study of the structure of genes and how they work to produce enzymes that influence an organism's development. David Hogness, also of Stanford, has shown that the methodology provides a way to find the location of specific genes within the chromosome (a chromosome is a very long molecule of DNA). This may give scientists deeper insight into when and where enzymes are made. These matters are worthy of attention, but I am confident that these as well as other problems of molecular biology can be solved by using other, safer experimental procedures—albeit over a longer period of time.

We have also been told that recombinant DNA research may offer us a number of practical benefits. Paul Berg has stated that "if the genes that produce the enzymes that make vitamins, antibiotics or hormones can be made to function in *E. coli*, then this bacterium, which can be grown in large quantity in the laboratory, could be used to produce these materials."

Berg has also said the research could yield "important benefits to expanding the world food supply." Our food supply depends upon the availability of fertilizer, which provides the nitrogen essential to plant growth. But abundant nitrogen exists in the atmosphere, and certain plants—legumes—are able to take advantage of it; they contain bacteria that convert the atmospheric nitrogen to forms plants can use. Recombinant DNA technology, according to its proponents, might make it possible to create major food crops with a similar ability.

In another area, Berg has asserted that "the isolation of genes put us at the threshhold of a new form of medicine, gene therapy, to treat crippling genetic diseases."

These claims, however, may be overstated. It may well be possible to produce vitamins or hormones such as insulin by means of genetic engineering, but commercial production of such biological chemicals has been possible for years. The idea of creating food crops nourished by atmospheric nitrogen is intriguing, but at the Miles International

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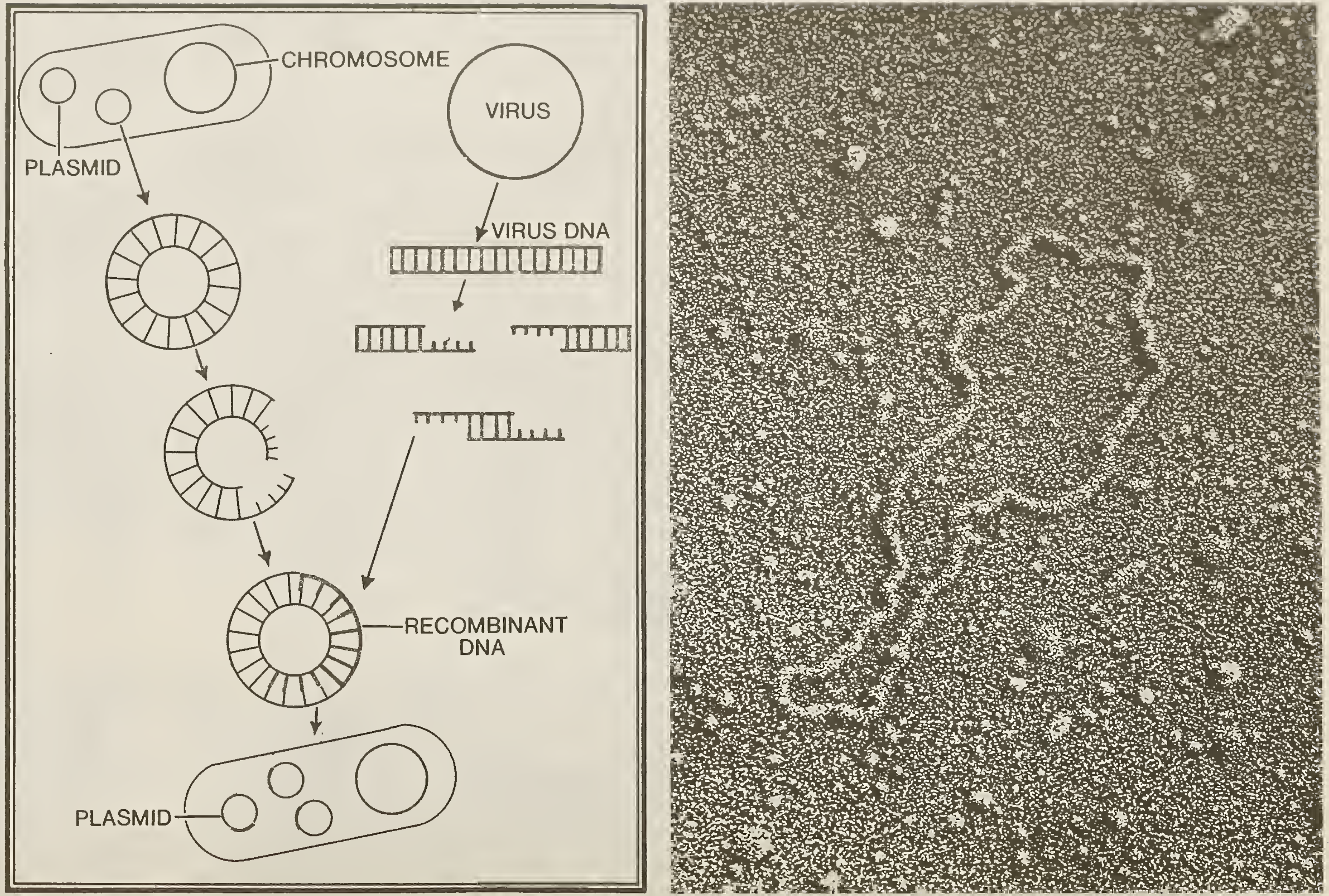


The recombinant process: In the diagram at left, ellipse represents a bacterium containing one chromosome (a large DNA molecule) and two plasmids (smaller circular DNA molecules). Large circle represents a virus containing long chainlike DNA molecules. After both plasmid and viral DNA molecules are isolated and treated with restriction enzyme, they break apart, a fragment of viral DNA joins the plasmid ring to form a new recombined molecule and the plasmid is reabsorbed by the bacterium, which multiplies without limit. At right, the closed loop of a recombinant plasmid, enlarged 230,000 times.

Symposium on recombinant molecules, held this June at the Massachusetts Institute of Technology, plant scientists reported not only that goals such as these are difficult and distant, but they are more likely to be achieved by the traditional methods of genetics rather than by the new molecular recombinant techniques. As for gene therapy, Berg himself says that "though simple and attractive in principle, this step has many pitfalls and unknowns, and these still have to be examined carefully before such therapy could be considered."

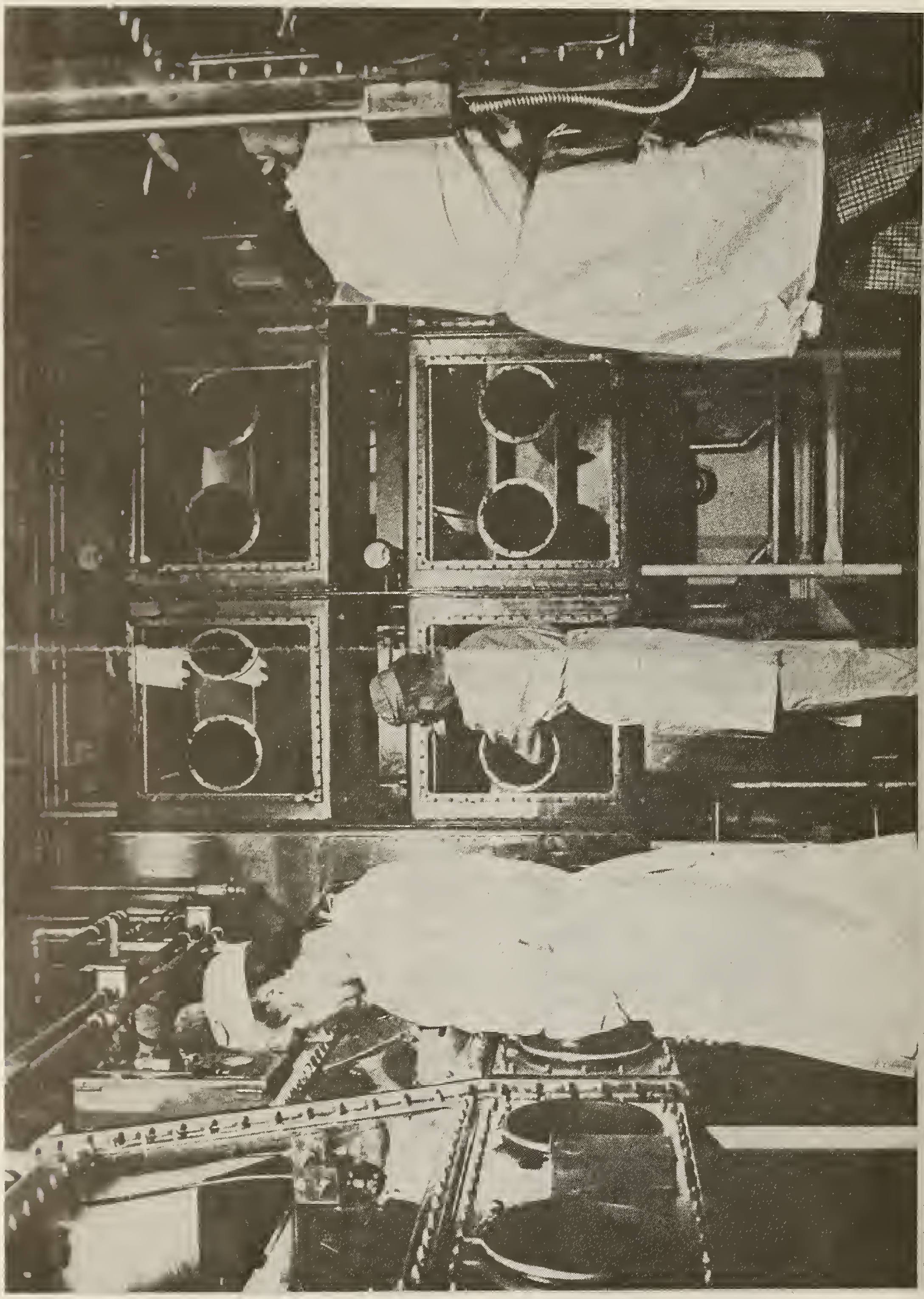
But to measure the true value of such potential benefits, we must weigh them against the hazards of this technology. The research involves many unknown factors beyond the control of the scientist. Since the plasmid and nonplasmid DNA fragments may combine in many different ways in a given recombinant experiment, it is necessary to create vast numbers of cells with unknown genetic alterations in order to obtain a cell containing a specific recombinant DNA. The probability of creating a dangerous genetic agent in the process is real, and there is no way to test for the danger. The scientist does not know what he has done until he has analyzed the newly created cells—at which point it may be too late.

Furthermore, because recombinant DNA's can reproduce themselves in their host cells, they can become permanent residents wherever the host cells are found, and once released into the world, it would be impossible to control them. In this respect, they are quite unlike any other man-made hazard. If we stop manufacturing DDT or Red Dye No. 2, they will cease to be problems. The air and waters of the earth will gradually return to normal if we stop pouring wastes into them. Most problems of modern technology build up visibly and gradually and can be stopped before a critical stage is reached. Not so with genetically altered bacteria; a single unrecognized accident could contaminate the entire earth with an ineradicable and dangerous agent that might not reveal its presence until its deadly work was done.

Dr. Robert Sinsheimer, chairman of the Biology Division of the California Institute of Technology and chairman of the editorial board of the Proceedings of the National Academy of Sciences, has warned that "what we are doing is almost certainly irreversible. Knowing human frailty, these structures will escape, and there is no way to recapture them." Erwin Chargaff, Professor Emeritus of Columbia University and a recipient of the National Medal of Science and other honors for this work on DNA, has written, "I should say that the spreading of experimental cancer may be confidently expected."

The widespread use of *E. coli* bacteria in this new genetic research increases its dangers. From the point of view of public health, this bacterium is the worst of all possible choices. It is a normal inhabitant of the human digestive tract and can easily enter the body through the mouth or nose. Once there, it can multiply and remain permanently. Thus every laboratory working with *E. coli* recombinants is staffed by potential carriers who could spread a dangerous recombinant to the rest of the world. *E. coli* is found in the sewage that flows through all of our communities; it lives in all warm-blooded animals, in insects and in fish; it is present on grass and vegetables and in water.

In addition to its ubiquitousness, *E. coli* is very promiscuous and during mating has a formidable propensity to transfer from one cell to another plasmids containing genetic information. This exchange can occur even with some other types of bacteria. Dead *E. coli* can also transfer their genes. Even weakened strains of *E. coli,* which re-



"Physical containment" safety: In a simulation of procedures used to prevent escape of dangerous organisms, scientists manipulate equipment inside steel-and-glass cabinets.

A single unrecognized accident could contaminate the entire earth with a dangerous and ineradicable agent that might not reveal its presence until its deadly work was done.

quire special laboratory conditions for growth, are able to pass on dangerous recombinant genes to healthier bacteria. Scientists choose *E. coli* for use in genetic engineering research because more is known about its genetics than about those of any other cell, and they do not wish to spend the time necessary to study the genetics of a substitute. The few years required to study such an alternate loom large to the scientist with his eye on the Nobel Prize.

For the public at large, however, the difference between 20 or 22 years in the achievement of some hypothetical benefit cannot justify the risks. Consider, for example, the fact that DNA from cancer viruses has already been introduced into a weakened form of *E. coli* (the ability of this form to survive in the human intestine is disputed at present). Suppose a laboratory technician accidentally pours a culture of these bacteria into a sink—not an unlikely occurrence. In the trap of the sink, or farther on in the sewage system, malignant properties are transferred from the laboratory bacteria to normal *E. coli*. The sewage, with the bacteria containing cancer genes, is eventually discharged into the sea near a shellfish bed. People in distant places eat the shellfish and the bacteria take up residence in their intestines and are spread from person to person. In the individual the bacteria can transfer recombinant DNA containing cancer genes to human cells. The result—cancer, normally not infectious, is spread in epidemic proportions by normally harmless bacteria.

Another possibility: The Biological Laboratory of Harvard University is now infested with a small Egyptian ant that has resisted all attempts at extermination. A laboratory specifically designed to contain dangerous recombinant forms of *E. coli* (the laboratory to which the Cambridge City Council objects) is expected to be constructed in this building. Suppose an Egyptian ant, carrying normal *E. coli* bacteria, enters the containment laboratory. It crawls in and out of a sterile container to be used later for growing weakened *E. coli* containing cancer genes. The ant contaminates the container with normal *E. coli*, which picks up the dangerous genes during a subsequent experiment. A small spill during the experiment releases some of these bacteria into the air, and they are inhaled by the scientist as he cleans up the spill. No one suspects any danger, since the bacteria were thought to be "safe." Some years later, the scientist and members of his family develop cancer, and a general rise in cancer incidence is noted.

The introduction of genes from cancer viruses into *E. coli* is only one of a number of ways in which cancer might be spread by recombinant DNA. Biologists suspect that the DNA of all normal animal cells contain inactive cancer genes. Cancer may normally arise when these genes are activated by some unusual disturbance such as tobacco tar or air pollutants. Similarly, the transfer of a supposedly harmless recombinant DNA from *E. coli* to a human cell could act as a monkey wrench in the regulatory machinery that controls the cell's dormant cancer genes.

It is possible, intentionally or unintentionally, to construct highly dangerous agents of other types, worse than anything yet envisioned in biological warfare. For example, *E. coli* or other bacteria that normally live in man and animals could be given the ability to produce deadly toxins, such as that of botulism. Protection by immunization would be out of the question. It is quite possible that an agent of this type might arise inadvertently, since in many experiments the nature of the genes implanted into a new host is unknown. The sudden appearance of new disease-causing agents is a threat not only to man directly but to the animals and plants on which he depends for food and oxygen, not to mention the purely esthetic aspects of the environment.

There is even danger in purposely-designed recombinant agents. Suppose, for instance, that drug companies are eventually successful in producing insulin or other products by growing genetically-engineered *E. coli* on an industrial scale. The slightest leak or other accident would constitute a major

Most laboratory accidents are not due to faulty equipment but to human error, and the possibility of human error increases with the eagerness of scientists to push for results.

human hazard. If bacteria producing insulin were to find their way into a human host, the result could be insulin shock and very likely death. The production of other drugs or industrial products in the human intestine is likely to be equally dangerous.

Not all the danger of recombinant work lies in cancer or in strange new diseases. There are also the hazards of success. The aim of genetic engineering is to speed up the evolution of chosen organisms. In so doing the slowly developing balance among living systems may be changed in sudden and decisive ways. What will happen if, for instance, a food crop were to be given the toughness and resistance of weeds, plus the ability to grow in a wide variety of habitats? The resultant vegitation might wipe out all other plants with lesser advantages, as well as the animals that feed on them—a drastic ecological change might be the price of more rice. Natural evolution works gradually on all species at the same time. If we undertake to control evolution ourselves, we cannot hope at once to control the myriad factors that make the world habitable.

Scientists have been slow to acknowledge all the dangers inherent to genetic manipulation. I myself must admit that, while I felt uneasy about future hazards when I carried out experiments on bacterial transformation 15 years ago, I did not ponder the full scope of the problem until recently. But today many of the hazards are immediate, and biologists can no longer shirk their social responsibility.

The question of hazards was discussed at a special meeting of the Advisory Committee to the Director of the National Institutes of Health called early this year by Dr. Donald S. Fredrickson. In addition to the members of the Advisory Committee, he invited a group that included David Bazelon, Chief Judge of the District of Columbia Court of Appeals, Peter Hutt, former counsel of the Food and Drug Administration and Philip Handler, president of the National Academy of Sciences. Most of the scientists present at this meeting defended recombinant DNA technology, citing all the benefits to be realized by basic biological research. Among them were David Baltimore from Massachusetts Institute of Technology, Paul Berg and David Hogness from Stanford, Donald Brown from Carnegie Institution of Washington and Charles Thomas from Harvard Medical School.

On the other side of the aisle were a few lone critics. A constant voice was that of Robert Sinsheimer. He emphasized that a major problem of recombinant DNA technology is the crossing of genetic barriers between species, an activity that opens an unfamiliar area of biology. He also has pointed out that scientists have ignored "the potential broader social or ethical implications of initiating this line of research—of its role as a possible prelude to longer range, broader scale genetic engineering of the fauna and flora of the planet, including, ultimately, man. . . ." In a philosophic sense Sinsheimer has said, "Would we wish to claim the right of individual scientists to be free to create novel self-perpetuating organisms likely to spread about the planet in an uncontrollable manner for better or worse? I think not." Robert Goldstein of the Harvard Medical School and Allen Silverstone of Massachusetts Institute of Technology have also been among the few who have pleaded for caution.

Those who have carried out the research on recombinant DNA and favor its continuation are respected scientists from large universities, and they constitute an informal but powerful lobby. I feel, however, that there is a large silent majority of scientists who would speak out for a sane solution if given the opportunity.

The safety guidelines put forth by the National Institutes of Health have been hailed eagerly by workers in the recombinant DNA field who wish to express their public concern. But in the meetings and discussions that preceded publication of the guidelines the focus remained on safety measures; scarcely a voice raised the fundamental question of whether the research should continue at all. Rather, on the implicit assumption that the work ought to proceed, they devoted painstaking effort to the formulation of safety precautions to prevent accidents. Here there was some controversy, the participants being divided between those who wanted lax rules, and those who wanted still laxer rules. The viewpoints varied with the participants' degrees of vested interest in recombinant research, and most had been involved to some degree. As Professor Chargaff said, "... the incendiaries formed their own fire brigade." In pointing out that the decisions have all been made by scientists, Senator Edward Kennedy, Chairman of the Senate Subcommittee on Health, objected that "the factors under consideration extend far beyond their technical competence." There has been no significant input from experts in public health, ecology, sociology, ethics or philosophy, and no effort has been made to inform the public of the dangers or to solicit popular opinions.

Briefly, the guidelines have two basic features. The first is physical containment. This means that the laboratory must be equipped to minimize the chance that experimental organisms might escape. The laboratory is kept under negative pressure so that air does not escape but is pumped out through filtered vents. For more hazardous experiments the worker must shower before entering or leaving the facility. The second feature, called biological containment, involves the use of enfeebled organisms so that if some do escape, they cannot survive in the outside environment. None of the precautions is foolproof. Significant containment measures are required only for the more obviously dangerous types of experiments. In a discussion of safety at the recent Miles Symposium on recombinant molecules, the experts were divided between those who feel that physical containment is unreliable and those who do not trust biological containment. Perhaps both are right.

In the course of 25 years of Army research on biological warfare agents at Fort Dietrich, equipped with the highest level of physical containment facilities, there were 423 accidental infections and three deaths. Accidents due to human error are inevitable, all the more so because scientists under pressure become inured to taking risks. The temptation to do things the easy, quick way instead of the safe way is hard to resist. In the case of recombinant DNA, it is an all or none situation — only one accident is needed to endanger the future of mankind.

Biological containment is a new concept in laboratory safety, one that has not really been tried. The rules therefore involve guesswork, and some are arbitary. For instance, one of the National Institutes of Health rules states that an experiment using recombinant *E. coli* is safe only if no more than one out of 100 million of the bacteria is able to survive outside the laboratory. (It should be noted that 100 million is a small number as laboratory bacteria go.) This raises some difficult questions. In testing the safety of an *E. coli* strain how much time should be allowed for all but one of the 100 million bacteria to die? Since different recombinant DNA's inserted into the bacteria may affect their survival, how can they be tested in advance, without incurring a risk during the test? Obviously it is impossible. Dr. Stanley Falkow of the University of Washington School of Medicine has said, "It is also clear from our studies that a carried plasmid [i.e., a plasmid inside a bacterium] may have a profound effect on the survival and carriage of E. Coli...it may not be too far-fetched to suggest that some DNA recombinant molecules could profoundly affect the ability of [weakened] *E. coli* to survive and multiply in the gastrointestinal tract." Moreover, how can all the possible bacterial growth conditions outside the laboratory be simulated for the test? The National Institutes of Health committee agreed that there are no objective answers to these questions.

It is generally known that most laboratory accidents are not due to faulty equipment but to human error, and the possibility of human error inincreases with the eagerness of scientist to push for faster results. Thus even if scientists swear to adhere to the guidelines, which have no force of law, I doubt very much that they can be effective. Harvard biology professor Carroll Williams is quoted as saying, "Scientists are racing for advantage and priority in a hotly competitive field and are likely to do what they can to win the race. The competition in this field is really fantastic. One scientist even told me, 'If we don't get the containment facility we want, we'll just reclassify our experiments from a higher to a lower security requirement.' . . . I believe him."

The pace of recombinant DNA research is increasing daily. At a time when research funds are increasingly difficult to obtain, the U.S. Government has just announced the availability of contracts in this field. Students hoping to assure their future are flocking to centers of recombinant research — Stanford, Boston, Paris, Stockholm, Geneva, London—and biologists everywhere are turning to the new techniques. Reflection about ultimate values or social priorities is not part of the scene.

In the development of the atom bomb during the war there seemed to be a compelling rationale for its urgency and secrecy, even though many physicists now bemoan the actions they themselves favored at the time. There is no such compelling reason to rush into recombinant DNA research, and I believe we should do everything possible to halt its current frenzied pace. The lure of the Nobel prize is a strong force motivating scientists in this field. I would suggest that the Nobel Committee announce that no awards will ever be given in this area. At the same time, I would urge the National Academy of Sciences to call for an immediate world-wide moratorium on recombinant research so that the issues can be examined more carefully and safety measures can be developed in a thorough manner rather than in the current crash-program atmosphere. (Such a moratorium might not be wholly enforceable, but it would stop the research in many places, and it would help to arouse public awareness of the issue.) A safer bacterium than *E. coli* can be studied for future research use. Laws can be enacted to forbid secret recombinant research by drug companies or others and to make it illegal to conduct recombinant experiments outside of certified laboratories. Most important, the people of the world will have the opportunity to decide whether they want genetic engineering research to continue at all.

In my view, recombinant DNA technology is so overpowering and far reaching in its potential for harm that decisions on how to handle it must not be left to the scientists alone. At the Asilomar conference, Alexander Capron of the University of Pennsylvania Law School told the assembled recombinant researchers: "As crucial as your research seems to you to the achievement of progress, you should be prepared for the eventuality that the public may not agree."

It would make sense, certainly, for Congress to set up a National Biohazards Commission analogous to the Atomic Energy Commission, with legal authority to evaluate, license, supervise and inspect all activities that may subject the public to biological hazards of any kind. The members of the Commission should of course be independent of the biological Establishment and should represent a broad spectrum of the public. In addition, I hope that the United States will take the lead in forming an international council on biohazards in order to establish a uniform worldwide policy.

I am aware that these suggestions may be regarded in some circles as a threat to freedom of research. Freedom to search for truth has always been a precious academic right, and every scientist jealously guards it. But this venerated 19th-century idea can no longer be entertained in the light of this new technology. A new dimension has entered the picture—the element of risk for humanity at large. We must ask, with Professor Chargaff, "Have we the right to counteract, irreversibly, the evolutionary wisdom of millions of years, in order to satisfy the ambition and the curiosity of a few scientists? This world is given to us on loan. We come and we go, and after a time we leave earth and air and water to others who come after us. My generation...has been the first to engage, under the leadership of the exact sciences, in a destructive colonial warfare against nature. The future will curse us for it." ■

Senator JAVITS. By way of views of my own, we are really at a watershed of whether the Government can or cannot adjust to the awful implications of science for the death of man. or the life of man. That is the question. Shall man have life, or shall man have death?

This begins to adventure into that unbelievably dark and subtle area, because we either can be on the threshold of a new frontier and a breakthrough in respect to genetics and all that it implies, or we can be on the threshold of a biological holocaust for which, like the Pennsylvania disease of the American Legion, we have absolutely no defense, and indeed, no knowledge.

I hope the public will realize that, that while we run risks, we run risks perhaps in order to save hundreds of millions of lives. And that I gather is the thrust of the NIH guidelines.

Now, as a person in public life, I would like to inform our witnesses what I think the public wants to know. It wants to know whether private companies concerned about their own affairs, their trade secrets, their research objectives, who are the recipients of contracts, et cetera, and whether universities and other research institutions who are going to deal in this field, require special regulation or licensing.

The whole concept of Government regulation must change. This is a matter of the public safety, let alone the public health.

Second, can industry develop the performance standards to demonstrate that it is policing itself to protect the public's health and safety, considering the lethal nature of the subject or the subjects of these experiments and the lack of knowledge which we have about controlling them and protecting the public from them.

And the public wants to know whether the Department of Defense, the Department of Agriculture, the CIA, the NIH, and other agencies are exerting sufficient vigilance, and do they really know what is going on, and how infinitely dangerous is this type of research because of a lack of knowledge.

I believe, gentlemen, in your presentations to us you ought to bear in mind that in this case doctrinaire assertions about Government control and Government regulation and Government interference with private enterprise just will not hold.

As we say about war, it is too serious to be entrusted to generals. The same is true here. It is too serious to be entrusted exclusively to corporate executives, or even to researchers.

So I hope that the sheer solemnity of this unknown area which we face will dictate a degree of courage and boldness on the part of those who testify before us, especially the Government people who testify before us, which is apposite to so new, so dangerous, yet so promising prospect as is presented by this type of research.

Senator KENNEDY. Dr. Fredrickson.

STATEMENT OF DR. DONALD S. FREDRICKSON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH; ACCOMPANIED BY DR. WILSON K. TALLEY, ASSISTANT ADMINISTRATOR FOR RESEARCH AND DEVELOPMENT, ENVIRONMENTAL PROTECTION AGENCY

Dr. FREDRICKSON. Mr. Chairman and Senator Javits, it is a pleasure for me to appear before you today to discuss the guidelines to which you have made reference.

Mr. Chairman, if you have no objection, I would like to submit my complete statement for the record and concentrate on a few parts of it in detail.

Senator KENNEDY. Without objection it will be made part of the record at the conclusion of your testimony.

Dr. FREDERICKSON. In June, the National Institutes of Health, with the approval of the Secretary of HEW and the Assistant Secretary for Health, issued guidelines to govern NIH-supported research on recombinant DNA molecules. Accompanying the guidelines was a document describing in detail the issues which the Director of NIH considered in reaching the decision to release the guidelines.

These guidelines, governing research conducted at the laboratories of NIH as well as projects supported by grants and contracts, delineate stringent safeguards for the conduct of experiments involving the production of recombinant DNA molecules and their insertion into organisms such as bacteria.

The object of the guidelines is to minimize the risks associated with recombinant DNA research—primarily through a series of procedures aimed at physical and biological containment of possibly dangerous organisms—while permitting research of great potential benefit to mankind. The NIH guidelines replaced the recommendations from the 1975 Asilomar Conference on Recombinant DNA Molecules, which permitted research under less strict conditions.

Recombinant DNA molecules are formed in the laboratory from recombination of segments of deoxyribonucleic acid, the material that determines the hereditary characteristics of all living cells. These techniques, permitting genetic information from quite different organisms to be combined, have a remarkable potential for furthering the understanding of fundamental biochemical processes of both lower and higher organisms.

As has been indicated, recombinant DNA research has strong potential in medicine as well as in science and technology generally. In medicine it is capable of providing hitherto unobtainable knowledge of the organization and expression of genes in health and disease. It possibly may also permit economical production of important medicinals. Potential benefits in agriculture and industry include more abundant crops and synthesis of industrially important biochemical agents such as enzymes.

There are risks, however, as well as potential benefits in this new research. For example, bacteria with transplanted genes may prove hazardous to man or other forms of life. Like many of the potential benefits, these risks remain speculative, for there is still scanty evidence that genes from one form of life can be expressed in any other form.

We must assume, however, that they may be. Thus our present state of knowledge dictates strict controls on this form of experimentation.

The NIH guidelines prohibit certain types of experiments—those, for instance, that might produce disease germs with increased resistance to antibiotics. Other experiments will go forward under special safety conditions. The guidelines have a definitive administrative framework for assuring that safety is an essential and integrated component of research involving recombinant DNA molecules.

The section dealing with roles and responsibilities sets forth a developed review structure involving the principal investigator, local biohazards committees, and the NIH Advisory Committee, as well as peer review apparatus already in place. The guidelines now provide extensive opportunity for advice, from the local to the national level.

Several levels of review and scrutiny are provided, insuring the highest standards for scientific merit and conditions for safety. We believe these provisions will afford protection, with a wide margin of safety, to workers and the environment while permitting this type of research to proceed. And the NIH is sponsoring additional experimental work to determine possible hazards and new safety practices and procedures.

Senator KENNEDY. Doctor, can you tell us specifically who these guidelines apply to today?

Dr. FREDERICKSON. The guidelines of the National Institutes of Health apply today to all grantees or contractors of the National Institutes of Health, as well as intramural scientists in Bethesda. They have also been adopted by the National Science Foundation for all their grantees or contractors, and for research supported or conducted by the Energy Research and Development Administration.

The Defense Department has indicated that they would adopt the guidelines were they conducting any such experiments.

Senator KENNEDY. What does that mean? Does that mean they are, or they are not?

Dr. FREDRICKSON. According to information provided us they are not at the present time engaging in recombinant DNA research.

Senator KENNEDY. So as I understand it, they will conform to the guidelines if they do?

Dr. FREDRICKSON. Yes; they have so indicated.

Thus, all of the Government agencies that are conducting this research, with the exception of the Department of Agriculture, all other agencies now conducting or supporting research in the Government are in accordance with them.

Senator KENNEDY. What is the reason for the Agriculture Department not conforming? What do they tell you?

Dr. FREDRICKSON. We have heard from the Department that they are considering the adoption of the guidelines, but they have activities relative to this research in several different divisions, and they have not yet completed the administrative review which they require in order to be certain how they will adopt them and implement them.

Senator KENNEDY. Do you think they should conform to the guidelines?

Dr. FREDRICKSON. I think they should, and I think they will.

Senator KENNEDY. Do you think they should conform to them immediately?

Dr. FREDRICKSON. Yes; I think they should.

Senator KENNEDY. Will you inquire again from the Secretary? We certainly ought to write to the Secretary of Agriculture today, indicating your testimony, and inquiring when he is going to respond.

Senator JAVITS. Mr. Chairman, I would suggest that first, I talk to the President, or someone representing the President. I will call this Agriculture situation to his attention, and then let us see what that calls for from us. It may call for another letter to the President. But I will join you in getting after Agriculture, at least to find out why they have so responded.

Senator KENNEDY. Dr. Fredrickson, to get back to the point in this part of your testimony, about the importance of monitoring, which obviously we feel is extremely important, I am sure you are aware of what we have previously heard in testimony before our committee in terms of monitoring, and the basic weakness of the monitoring system.

This has been true of the FDA, in monitoring scientific information that has been made available to them, that has been supplied by some of the independent research groups and companies that were doing work for the drug companies.

Then we heard in terms of the EPA a similar situation which obviously is a matter of very serious concern, for the obvious reasons that it is going to be impossible to make a sound, scientific decision in the interest of the public, unless you are going to have accurate scientific data.

Today we are releasing a study and report that was done by the Subcommittee on Administrative Practices and Procedures extending this concept to the National Cancer Institute, which raises similar problems in terms of monitoring. A very positive and constructive response by Dr. Rauscher, that discusses the steps that they are taking to meet those particular areas of failure, indicates that those areas have not had the kind of tight oversight as he would have liked to have seen.

He is outlining, in some detail, what the Cancer Institute is prepared to do.

I will make Dr. Rauscher's response a part of the record.

[The material referred to follows:]

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July 6, 1976

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Building 31, Room 11A52
9000 Rockville Pike
Bethesda, Md. 20014

Dear Dr. Rauscher:

The Subcommittee on Administrative Practice and Procedure has been looking into the operation of the National Cancer Institute's Carcinogenesis Program. In April I transmitted to you a memorandum by Dr. Saffiotti raising certain questions regarding the program; I have received responses to the charges in that memorandum from both you and Mr. Benno Schmidt, and I appreciate the thorough nature of your replies.

In the enclosed Report prepared by Subcommittee staff from interviews with NCI professional staff and from a review of memoranda and other records, a number of problems have been identified independent of the discussion in Dr. Saffiotti's memorandum. A number of the matters raised in this Report appear to me to go to the heart of the effectiveness of the NCI's Carcinogenesis Program.

The Subcommittee staff has proposed five recommendations stemming from its inquiry, as follows:

1. The NCI should dedicate necessary resources and personnel to ensure adequate safety for laboratory personnel.

2. The NCI should undertake a comprehensive management analysis of the operation of the Frederick Cancer Research Center.

3. There should be unannounced and more frequent and thorough site visits to the bioassay testing laboratories.

4. Monitoring of the prime contractor for bioassay testing should be substantially intensified.

5. A review of the "fee award" contract should be initiated in light of questions raised by NCI staff and the Army Management Training Agency's recent audit.

In light of the importance of NCI's bioassay testing program, which was established to provide guidance to the public and to other federal agencies on chemicals in the environment and in food which may cause cancer, I would like to have your responses to the issues raised in the Staff Report and specifically to these recommendations. I believe that our findings and conclusions will assist the National Cancer Institute in its efforts to conquer and combat cancer, and I appreciate your cooperation.

Sincerely,

Edward M. Kennedy

Staff Report

Subcommittee on Administrative Practice and Procedure
on
The Carcinogenesis Program of the National Cancer Institute

Overview

In recent years, the National Cancer Institute has assigned almost 500 chemical compounds for animal bioassay testing to university and commercial laboratories and to the Frederick Cancer Research Center. The purpose of Bioassay testing is to determine whether the chemicals cause cancer.

Last January, shortly after the beginning of the Subcommittee's investigation of the Environmental Protection Agency, it became apparent that pending decisions at EPA on regulatory action involving some 70 pesticide compounds are heavily dependent upon the results of NCI's bioassay tests of those compounds.

In addition to EPA, other agencies such as the Occupational Safety and Health Administration, the Food and Drug Administration, and the Consumer Product Safety Commission, also rely upon NCI's bioassay testing in their regulatory activities designed to protect both the American public and the environment.

It is for that reason that the Subcommittee staff was charged with investigating NCI's bioassay testing program, which is administered by the Institute's Carcinogenesis Program.

Numerous interviews of Carcinogenesis Program personnel and reviews of Program files indicate that, while the bioassay testing program has improved over the past few years, the program has continued to suffer from serious problems: (1) lack of safety; (2) poor performance in testing; (3) lengthy delays in reporting of test results; (4) inadequate monitoring of testing; and (5) questionable contractural arrangements.

These problems may be symtomatic of more basic issues revealed in the "Survey of Professional Staff Attitudes" conducted Institute-wide in 1974. Among the survey findings on "attitudes" were: (1) "A widespread lack of confidence in scientific acuman of the 'decision making' hierarchy" (47 percent of those surveyed); (2) "The deterioration of communications and management control and coordination vertically and horizontally within the Institute" (59 percent of those surveyed); and (3) "Lack of participation in program management" (26 percent of those surveyed).[1]

The survey has not been repeated in the past two years and, therefore, it is not known whether these "attitudes" have changed for the better or for the worse.

Most of the problems in the bioassay testing program cited in this Report developed in 1972 and 1973, when there was a substantial expansion of such testing. At that time, the Carcinogenesis Program was contracting directly with private laboratories for bioassay testing of chemicals, and Program scientists were responsible for monitoring and directing the work of these laboratories. However, while funds for this extramural bioassay testing increased at a rapid rate, the number of Program personnel involved in managing and monitoring the work of the private laboratories did not increase in proportion to the growth of the bioassay testing.

The program was further expanded in 1973, when the decision was made to utilize the Frederick Cancer Research Center (FCRC), a NCI facility, for additional bioassay testing. The FCRC is operated for the Institute by a private research firm, Litton Bionetics, Inc., through a contract from the Office of the Director of NCI. Initial plans called for FCRC continuously to maintain a total of 60 chemicals on bioassay test for the Carcinogenesis Program.

In 1973, a report expressing concern over "the personnel crisis in the Carcinogenesis Program" was submitted to the Director of NCI.[2] Subsequently, the Program was advised to hire a prime contractor to manage and monitor the private laboratories as subcontractors. A prime contractor, Tracor-Jitco, assumed these responsibilities in May 1974. Carcinogenesis Program scientists were assigned to monitor the prime contractor.

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[1] Manpower Management Program, Contract Activities, Survey of Professional Staff Attitudes (Submitted to the NCI Executive Committee) October 3, 1974.

[2] "Documentation of the Personnel Crisis in the National Cancer Institute's Carcinogenesis Program," prepared by Dr. Umberto Saffiotti, Associate Director for Carcinogenesis, for the Director of NCI, July 1973.

A year later, in June 1975, Carcinogenesis Program managers acknowledged that there still were problems with the bioassay testing and requested that a mangement analysis of the prime contractor be conducted. The U.S. Army Management Training Agency (AMETA) was chosen to perform the recently completed study. AMETA's findings are contained in this report.

In a memorandum[3] to the Director of NCI, dated May 3, 1976, Dr. Umberto Saffiotti resigned his position as Associate Director for Carcinogenesis (Carcinogenesis Program), complaining of NCI policymaking and a lack of support for the Program.

Upon receiving a copy of Dr. Saffiotti's memorandum, the Chairman of the Subcommittee requested comment from the Director of NCI[4] and the Chairman of the President's Cancer Advisory Panel[5] on issues raised in the Saffiotti memorandum. Their responses to the Chairman of the Subcommittee indicated that the Saffiotti resignation was a result of differing opinions concerning program management, and that the Carcinogenesis Program had been given adequate support.[6,7]

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[3] Memorandum from Dr. Umberto Saffiotti, Associate Director for Carcinogenesis, to the Director of NCI, April 23, 1976, on Saffiotti's resignation.

[4] Letter from Senator Edward M. Kennedy, Chairman of the Subcommittee, to Dr. Frank J. Rauscher, Jr., Director of the National Cancer Institute, April 26, 1976.

[5] Letter from Senator Edward M. Kennedy, Chairman of the Subcommittee, to Mr. Benno Schmidt, Chairman of the President's Cancer Panel, April 26, 1976.

[6] Letter from Mr. Benno Schmidt, Chairman of the President's Cancer Panel, to Senator Edward M. Kennedy, Chairman of the Subcommittee, May 1, 1976.

[7] Letter from Dr. Frank J. Rauscher, Jr., Director of the National Cancer Institute, to Senator Edward M. Kennedy, Chairman of the Subcommittee, May 3, 1976.

Dr. Saffiotti's resignation occurred during the Subcommittee's investigation of the Carcinogenesis Program, and the views contained in this Report, while corroborated in part by Dr. Saffiotti, were derived independently and from sources other than Dr. Saffiotti.

Problems

1. Lack of Safety

A Litton Bionetics internal memorandum, dated April 15, 1976, states that the bioassay testing facility at the FCRC--

> is substandard and constitutes a significant threat to personnel and experimental integrity throughout (the facility)...(E)ven the very minimal personnel restrictions previously imposed are not being followed by the people in the Quarantine Section of the facility. This must be corrected, for in not utilizing protective clothing and in entering and leaving the facility at will, these people are greatly increasing the risk of...widespread chemical contamination...Far worse is at stake with chemical contamination...for this represents a clearly demonstrated risk to personnel. To ignore it would be immoral and could result in serious legal repercussions.[8]

Dr. Charles Warner, safety monitor for the Carcinogenesis Program, is critical of the prime contractor for not having a fulltime safety professional to correct problems in the subcontractor laboratories. According to Dr. Warner, personnel at some of these laboratories have been exposed unnecessarily to cancer-causing chemicals.

Dr. Warner's evaluation of the prime contractor, dated March 1, 1976, stated:

> The staffs of the subcontractors institutions are very defensive about their safety procedures and practices and claim (unjustly) that attempts to change them would result in unreasonable expenditures of money and time.

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[8] Litton Bionetics, Inc., Frederick Operations Division, Inter-Office Memorandum from Dr. Richard H. Cardy, Acting Manager, Bioassay Research, to Dr. Robert Stevenson, General Manager, FCRC, April 15, 1976.

> It will require a full-time, 'shirt-sleeves' effort by the prime contractor to correct this misconception.[9]

As of June 15, 1976, the prime contractor has yet to commit a full-time position to monitor safety in the subcontractor laboratories.

2. Poor Performance in Testing

Last year, the Litton Bionetics management of the FCRC rearranged bioassay physical facilities known as "Project 8" at the Center against the advice of Carcinogenesis Program scientists. The consequences were considered disastrous.

In a memorandum dated March 17, 1976, Dr. Norbert Page, Chief of the Carcinogen Bioassay and Program Resources Branch, stated:

> Serious problems have developed that create considerable concern for further carcinogenesis testing at FCRC...Litton Bionetics management located the quarantine facility in the Bioassay area even though strong opposition was expressed by the NCI and Project 8 staff (Litton Bionetics own scientists). Pinworms have infiltrated the 'barrier' from the quarantine, resulting in the abortion of tests, delay of plans, closure of barrier, and a serious financial loss to the Government. Several studies have been jeopardized with the results possibly of questionable value.[10]

The problems at the FCRC also have delayed testing at the subcontractor laboratories, which depended on the FCRC for their supplies of experimental animals.

Proper care of animals used in the two-year-long bioassay tests is critical if such tests are to provide valid and meaningful results.

In a December 1975 memorandum, Dr. Thomas Cameron, the Carcinogenesis Program's monitor for animal care, was critical of the prime contractor's efforts in overseeing animal care at Hazelton laboratories, a subcontractor laboratory. Cameron wrote,

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[9] Prime Contract Monitor's Report, by Dr. Charles R. Warner, March 1, 1976.

[10] Memorandum from Dr. Norbert Page, Chief, Carcinogen Bioassay and Program Resources Branch, to Associate Director, Carcinogenesis Program, March 17, 1976.

> 2,400 rats were entered or maintained on study in severe violation of the prescribed space allocations. This was permitted, condoned, and, there is some suggestion, encouraged by responsible individuals of the prime contractor staff strictly as a budgetary gain.[11]

In a March 1976 evaluation[12] Dr. Cameron criticized the prime contractor again for not yet having corrected the overcrowding of animals at the Hazelton facility.

3. Lengthy Delays and Lack of Quality in the Reporting of Test Results

Dr. Robert Squire, Chief Pathologist for the Carcinogenesis Program, stated that while the prime contractor and its subcontractors have improved their efforts in preparing test results, some of the work continues to be done in an erratic way. According to Dr. Squire, about 25 percent of the animal tissue slides from subcontractor laboratories are poorly done, making accurate diagnosis of tumors extremely difficult.

Delays of as much as two and three years in the completion of bioassay test results by subcontractor laboratories have forced the Carcinogenesis Program to transfer some of this work from at least one subcontractor laboratory and the FCRC to other laboratories directly under contract with NCI.

4. Inadequate Monitoring and Management of Testing

Carcinogenesis Program scientists assigned to monitor the prime contractor say they are unable to devote sufficient time to this task because of other pressing responsibilities and, as a result, progress has been slow in improving the performance of the prime contractor and its subcontractors.

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[11] Prime Contract Monitor's Report, by Dr. Thomas Cameron, December 4, 1975.

[12] Prime Contract Monitor's Report, by Dr. Thomas Cameron, March 4, 1976.

In a March 1976 memorandum, Dr. Robert Squire said, "Tracor (the prime contractor) has failed to utilize pathology (test results) support contractors to assist in monitorship, verification and conduct of pathology. I have encouraged this--at no cost to Tracor contract."[13]

Dr. Thomas Cameron stated in a March 1976 memorandum that

> The director and the Deputy Director at TJ (Tracor-Jitco) persist in involving themselves in matters outside their spheres of capability or experience, e.g., animal cage design, animal allocations and logistics. This has consistently led to confusion and decision making delays. This situation has certainly conveyed to affected individuals outside the immediate program a sense of poor management.[14]

In a February 1976 memorandum, Dr. John Cooper, the Carcinogenesis Program monitor of the prime contractor's work in selecting chemicals for testing, wrote: "The contractor's performance is still average. Little initiative is being shown in systematizing the chemical selection process, and his activities remain largely uncoordinated.[15]

Dr. Norbert Page, project manager for the prime contractor, reported last December that "Scientific management still appears to be a weak area as evidenced by projects not getting completed, e.g., inhalation guidelines, water-treatment problems, etc."[16]

A report dated June, 1976, from the U.S. Army Management Training Agency (AMETA) audit team to Carcinogenesis Program managers stated: "The prime contractor's scientific management effort is deficient."

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[13] Prime Contract Monitor's Report, by Dr. Robert Squire, March, 1976.

[14] Note[12], supra.

[15] Prime Contract Monitor's Report, by Dr. John Cooper, February 13, 1976.

[16] Prime Contract Monitor's Report, by Dr. Norbert Page, December 1, 1975.

AMETA also indicated a need for improvement in the Carcinogenesis Program's management of the prime contractor. The AMETA report said that "the current NCI management concept does not lend itself to a management effort of this magnitude" and indicated that there is confusion within the Carcinogenesis Program and the prime contractor over individual responsibilities and decisionmaking.

In hearings before the Subcommittees on Health and Administrative Practice and Procedure on January 20, 1976, the Director of the NCI testified that "we (NCI) site visit (the laboratories) frequently and unannounced."[17]

However, Carcinogenesis Program managers and monitors have said that site visits to subcontractor laboratories are always announced, and are not conducted as frequently nor as thoroughly as is needed. They suggest that unannounced site visits would serve to provide added assurance for the integrity of the bioassay test results, as well as speedier resolution of problems.

5. Questionable Contractural Arrangements

In May 1974, the NCI entered into a "fee award" contract with Tracor-Jitco, the prime contractor. The contract provides for grading of the prime contractor's performance by Carcinogenesis Program monitors on a scale from zero to 100 percent; the higher the grade, the higher the fee awarded to the prime contractor.

Several of the Carcinogenesis Program monitors have said that, since they do not have time enough to monitor adequately the prime contractor, there is a tendency to give the prime contractor "the benefit of the doubt," perhaps resulting in an over-grading and overpaying of the prime contractor. Also expressed was the feeling that, while the purpose of the "fee award" contract is to encourage improved performance by the prime contractor, this type of remuneration may encourage the prime contractor unconsciously to exaggerate the accomplishments of its subcontractors.

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[17] Statement by Dr. Frank J. Rauscher, Jr., Director, National Cancer Program-National Cancer Institute, Public Health Service, Department of Health, Education, and Welfare, before the Subcommittee on Health, Committee on Labor and Public Welfare, and Subcommittee on Administrative Practice and Procedure, Committee on the Judiciary, United States Senate, January 20, 1976.

Another concern over the contract is that the prime contractor's fee also is determined by the number of chemicals it assigns for testing to the subcontractor laboratories. Carcinogenesis Program monitors and managers believe that this provision of the contract has forced the prime contractor to devote more attention to quantity rather than to quality of testing.

AMETA is likewise critical of this provision of the contract. AMETA stated in its report (June, 1976) that "the current prime contract scope of work and award fee structure are not compatible with the overall carcinogenesis bioassay program objectives."[18]

Conclusions

1. Inadequate provisions for the safety of personnel exposed to carcinogens at subcontractor laboratories and at the Frederick Cancer Research Center indicate that emphasis on this most important area has been severely lacking.

2. While performance in bioassay testing appears to have improved in general, such problems as those allowed to develop at the Frederick Cancer Research Center illustrate a serious lack of supervision and management of the private contractor hired to operate the facility.

3. Many of the problems cited in this report indicate a shortage of NCI personnel required for adequate monitoring of the bioassay prime contractor and the subcontractor laboratories.

4. Questionable provisions in the contract with the prime contractor for bioassay testing may be working to the detriment of the goals and success of that segment of the Carcinogenesis Program.

5. The Carcinogenesis Program is in a state of flux for the following reasons:

A. The Program is being reorganized and divided into a research program and a bioassay testing program.

B. The Army Management Training Agency audit team has recommended substantial changes in the NCI's mangement of the bioassay testing prime contractor, and in the prime contractor's management of the subcontractor laboratories.

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[18] In-Process Review, Study of Prime Contracting in the Carcinogenesis Bioassay Program, by the U.S. Army Management Training Agency, May 4, 1976.

C. There has been movement of several key professionals, formerly involved in the bioassay testing program, to other areas within the NCI.

D. The National Clearinghouse on Environmental Carcinogens, referred to by the Director of the NCI in his letter to the Chairman of the Subcommittees on May 3, 1976, is not yet fully operational.

This state of flux in the Program appears to have resulted in a feeling of uncertainty and lower morale among many of the Program staff.

Recommendations

1. The NCI should dedicate necessary resources and personnel to ensure adequate safety for laboratory personnel.

2. The NCI should undertake a comprehensive management analysis of the operation of the Frederick Cancer Research Center.

3. There should be unannounced and more frequent and thorough site visits to the bioassay testing laboratories.

4. Monitoring of the prime contractor for bioassay testing should be substantially intensified.

5. A review of the "fee award" contract should be initiated in light of questions raised by NCI staff and the Army Management Training Agency's recent audit.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

NATIONAL CANCER INSTITUTE

September 15, 1976

The Honorable Edward M. Kennedy
Chairman, Subcommittee on Administrative Practice and Procedure
Committee on the Judiciary
United States Senate
Washington, D. C. 20510

Dear Mr. Chairman:

Thank you for your letter of July 6 regarding the five recommendations derived from the staff report of the Subcommittee on Administrative Practice and Procedure on the Carcinogenesis Program of the National Cancer Institute. I will comment first on what we have done thus far with respect to these recommendations, and subsequently provide detailed comment on the report itself.

The first recommendation concerns National Cancer Institute (NCI) commitment to provide necessary resources and personnel for ensuring adequate safety. We concur that additional steps must be taken and have made the decision to provide for the following needs in safety and health management as they pertain to your letter and the staff report: (1) Safety personnel within the National Institutes of Health (NIH) will serve as consultants in a program which will improve present safety management and result in the introduction of new technologies as are required. (2) Funds for equipment and training of personnel at all relevant levels will be provided for by the NCI. (3) The prime bioassay contractor [Tracor Jitco, Inc.] has been directed to employ a qualified professional who will work full-time on health and safety management of subcontractor laboratories. Dr. Charles Warner of the NCI now has full-time responsibility for safety management of the bioassay subcontractors. He will work closely with the NCI Office of Safety and Dr. Emmett Barkley, who directs that office, and his staff, and with the NIH advisory consultant group mentioned in (1) above and the Tracor Jitco full-time safety officer. Announced and unannounced site visits will be carried out, the former to establish acceptable practices and the latter to assure compliance with safety regulations. The safety officer at Tracor Jitco has been directed to use outside consultants whenever necessary to resolve safety-related problems. Contracts will be awarded within the next month to initiate studies on the proper treatment of airborne and waterborne contaminants resulting from laboratory carcinogenesis studies. Additionally, feasibility studies and pilot studies relating to worker protection and protection of the immediate work environment are being initiated. The goal of these efforts is to develop an exemplary safety program that is second to none and one which is sufficiently practicable and feasible as to be applicable to all the laboratories that are in the business of chronic testing of chemical substances. The expectation from pending legislation and newly promulgated regulations is that chronic testing will expand rapidly, thus the possibility exists that many hundreds of additional people will be working in laboratories where carcinogenicity testing is performed. We feel, therefore, that in addition to providing adequate stewardship to those who are working on our studies we also have responsibility for the development and evolution of procedures which are strictly applicable to all carcinogen bioassay laboratories. Eventually the Division of Cancer Control and Rehabilitation and their Prevention Branch will become involved in technology transference to these other laboratories to ensure they are aware of our progress and we of theirs, and that we together have the most effective safety program possible.

The second recommendation states that NCI should undertake a comprehensive management analysis of the operations of the Frederick Cancer Research Center (FCRC). The FCRC, as your staff report points out, is operated by Litton Bionetics, Inc., under contract with the Federal government. They were awarded the contract as a result of a competitive procurement in which there were five bidders in the competitive range. A decision has now been made to recompete the contract within the next 12 months. A contract review committee has been established which will evaluate the science of the program and assess the effectiveness with which it is being carried out. Evaluation of program management will be critical in the overall assessment. Additionally, however, we have identified funds for the purpose of implementing your recommendation that a comprehensive management analysis be conducted. We will explore with the U. S. Army Management Engineering Training Agency (AMETA) the possibility of their conducting such a study. It would be desirable to use AMETA for this purpose since they have a background in the management of the Institute's carcinogenesis bioassay collaborative program. This management analysis would serve a useful purpose in the competitive contract award process.

The third recommendation states there should be unannounced and more frequent and thorough site visits to the bioassay testing laboratories. We agree with this recommendation and have in the last three months increased our monitoring of the prime contractor, including weekly meetings with the principal investigator at Tracor Jitco and his staff. Tracor Jitco has been directed to hire two additional senior scientists who will have responsibility for individual subcontracting laboratories and their programs. This is in addition to the safety monitoring as discussed under recommendation one, above. These scientists are directed to visit each bioassay subcontracting facility at least four times per year with at least one visit being unannounced. In addition, other scientists will be charged with responsibility for specific disciplines such as pathology, toxicology, and animal care to monitor each subcontractor facility as needed but at least once a year. Other personnel will make site visits as required by NCI staff. It is anticipated that NCI staff will frequently accompany Tracor Jitco personnel on site visits to subcontractor facilities. In addition, plans are under way to implement direct on-line reporting of subcontractor results to obviate current delays and to provide for up-to-the-minute reporting of progress, status, and results. Such information will enhance our knowledge as to which subcontractor needs to be site visited and when that visit should take place. In this way, we can improve the efficiency of our site visit activities.

Recommendation four directs that monitoring of the prime contractor be substantially intensified. As stated above under recommendation three, this has been done. In addition, we recently held a two-day retreat to discuss what the NCI expects of its prime contractor, Tracor Jitco. [Enclosed is a copy of the agenda of that meeting.] The meeting was successful, and it is now planned to schedule such meetings at regular intervals to ensure that Tracor Jitco staff have a full understanding of NCI directives and are working efficiently to carry out these directives.

Recommendation five states that the award fee contract should be reviewed in light of questions raised by NCI staff and the recent AMETA report. I am pleased to report that this review has been carried out and significant changes are being made in the contract in accord with the questions alluded to above. One of the most significant changes concerns modification of the award fee pool. The award fee pool is defined as the maximum amount of money available to the prime contractor in compensation for carrying out the activities as prescribed in the contract. The exact amount of money is determined by an award fee system where the contractor is rated on performance. Previously, the award fee pool was dependent upon the number of chemicals that were put on test. Given the current problem of backlog where hundreds of chemicals have already come off test and the need is to provide a report on these chemicals at the earliest possible date, the former system of controlling the award fee pool is inappropriate. This is in the process of being changed, and in addition we are restructuring the award fee evaluation system to provide for increased leverage for NCI staff by adding specific emphasis areas. These emphasis areas will be selected in advance for periods of four months to provide focus on those aspects of the program where greatest need exists. NCI staff are also developing additional evaluation criteria, again for the purpose of making NCI needs clearer to the prime contractor. All of these changes are intended to address the very serious problems that have been identified in your staff report and the AMETA report and are now considered fact. Additional aspects of the restructuring of the prime contract are mentioned under my comment on the staff report.

Comment on the Staff Report

The overview of the staff report makes a number of important points. The lack of safety, poor performance in testing, lengthy delays in reporting of test results, inadequate monitoring, and questionable contractual arrangements have, I believe, been dealt with in my above comments. The issue of lengthy delays, however, requires special mention. Plans are now being developed which are to accomplish two things of critical importance: 1) completion and verification of pathology on approximately 100 chemicals within the next 12 months, and 2) coordination of this with a reporting activity to keep pace with the accelerated pathology output. Additionally, our efforts to establish on-line reporting should solve the problem of inordinate delays for all chemicals entered onto test in the future. We are determined to use the most up-to-date technology for the creation of solutions for these types of problems. It is clear, however, that this task is not an easy one, but it is also clear that through the fine efforts of NCI program staff real progress is being made toward that goal. We are certainly not relaxed or over-confident, but we are hopeful and determined, and will do whatever needs to be done, to correct past deficiencies. It was stated in the report that the problems identified above may be symptomatic of more root causes as revealed by the "Survey of Professional Staff Attitudes" conducted Institute-wide in 1974. I would have to agree with that conclusion, as does the Director of our Division of Cancer Cause and Prevention, who requested in a memorandum dated August 20, 1976, that given the numerous organizational changes which have recently been made within that Division it would be appropriate that the Division be re-examined by repeating the above survey or by any mechanism which would assure objectivity and accurate analysis. This Division Director also stated his belief that the organizational changes and program changes have had a favorable effect on morale and on staff attitude, but added that his view could be considered biased and subjective. I am well aware of the great number of changes effected in the Division, both large and small, and concur with its Director as to the propitiousness of a follow-up survey. We have not yet decided how this will be conducted or precisely when it will be undertaken. Clearly it must be soon and it must be done well and objectively if the information is to mean anything at all. I can, however, assure you that we will proceed to determine in an objective way whether attitudes have changed for better or for worse.

Regarding the statement concerning a major increase in funds for extramural bioassay testing compared to a small increase in program personnel, I make the following comment: As you are aware, this has occurred in all of our program areas and endeavors, and has resulted in a tremendous burden on our staff. Our responsibilities were considerably increased by the National Cancer Act of 1971. Concurrently, our funding was increased, but staff was not. No one in the Institute is more acutely sensitive to this problem than am I. Nevertheless, it is true that we could have done more had the line management for bioassay brought to our attention what we now know to be the problem. Initially two years ago, when certain aspects of the acuteness of the problem became apparent, we developed the concept and implemented the Tracor Jitco prime contract. We were led to think that this was working and working well. The prime contractor got consistent high ratings from the program and we were repeatedly informed that all was going well. Apart from certain specific requests concerning pathologists and toxicologists on the staff, there was no cry for additional staff to run this program nor had other specific areas been clearly identified. Today the situation is different. The program is being managed by staff in a rigorous way where it is now possible to identify any and all deficiencies in a well defined way and in a manner that certainly will lead to alleviations of problems attributable to specific staff shortages. My staff does not yet know precisely what these needs will be, but I am confident of their capacity to identify and justify these needs in a fashion that will lead to rapid action.

The comments relating to the FCRC's bioassay activities are accurate, and this is a problem which will need resolution. It is anticipated that the steps outlined above concerning management review and recompetition of the contract will help. I think it would be inappropriate for me to make statements and promises at this point in time which might preempt the processes now planned.

The staff report mentions the 1973 memorandum by the former Associate Director of the Carcinogenesis Program entitled "Documentation of Personnel Crisis in the National Cancer Institute Carcinogenesis Program." This memorandum, with its attachments, was carefully worked out and specified a number of personnel needs in the entire program, with perhaps greatest emphasis on those areas outside of bioassay. Analysis of that memorandum and its supporting documents indicates that we have made progress in fulfilling the needs of the bioassay program and of environmental carcinogenesis. For instance, since 1973 we have added pathologists and a toxicologist, have increased our interagency activity because of its vital importance to the entire program, and are in the process of enhancing our outside advisory activities. I refer specifically to the National Clearinghouse on Environmental Carcinogens which will have broad advisory responsibilities for the bioassay program. This public forum should provide the means whereby all problems come quickly to attention, irrespective of whether they embarrass the Institute, rock the boat, or portend grief for other interests. We envisage this advisory body to constitute a national resource to be used by regulatory agencies and to ensure openness, candor, and appropriate visibility.

I feel it fair to say that our recent changes and modifications are providing a new thrust which is consistent with the letter and tone of your staff report and will provide for greater rigor, defensibility, and reasonableness of current program activities. We do, however, hope to remain fully flexible so as to make whatever adjustments appear necessary to assure effectiveness within the program and appropriate interface with other Federal agencies and relevant constituents of the private sector.

Regarding the comment on Dr. Saffiotti's memorandum and my response to it, I think it is not correct to say that it was our opinion that the bioassay program had been given adequate support. I certainly did not mean to convey that it had when, indeed, it was functioning poorly and when we were attempting to effect some significant changes within the total Carcinogenesis Program which ultimately led to the memorandum by Dr. Saffiotti. I tried to convey in my letter to you what some of the difficulties were and the fact that the evidence before me indicated these difficulties could not be remedied by implementing Dr. Saffiotti's request for additional staff. Indeed, it is absolutely fair to point out that just months earlier Dr. Saffiotti, at a meeting in his Division Director's office to discuss reports on bioassay, contended that other areas of the Carcinogenesis Program had higher priority than did bioassay, and that he could not support the recommendation that additional personnel be hired for the expressed purpose of getting the reports out more rapidly. Indeed, Dr. Saffiotti consistently complained of any effort outside of his immediate responsibility which attempted to correct some of the problems that were then beginning to come to light. He resisted these efforts on the basis that he felt he knew best. Events show I did not agree.

The next part of the report deals with then current problems. Statements concerning lack of safety have been dealt with above under the first recommendation, and I will simply emphasize that the prime contractor has been directed to commit a full-time position for safety and safety monitoring in subcontract laboratories. The report correctly indicates the reluctance of the prime contractor to establish such a position, but this has been insisted upon and will be implemented. The issue of poor performance in testing can only be dealt with by more intensified monitoring and by providing encouragement and impetus for outstanding performance. As pointed out elsewhere, we have taken positive steps that should result in improved performance. With respect to the FCRC facility, however, I must defer comment until we have completed our activities and come to a policy decision as to the role FCRC is to play within the bioassay testing program.

Regarding lengthy delays and lack of quality control, these are matters already discussed. The delays have resulted in an enormous backlog of chemicals which are now off bioassay but have not been subjected to pathology or pathology verification and, of course, have not been properly reported. Steps are being taken now to involve support contractors, and plans are developing where we expect to complete pathology on 100 chemicals within the next 12 months. A parallel interacting effort will be established to ensure that these results are promptly reported. The situation of the backlog cannot be tolerated, and we must use all those resources available to us to rectify this serious problem. I am very pleased to report that Dr. Robert Squire and his staff have made excellent progress toward the development of approaches and plans to utilize all available resources for the purposes of dealing expediently with the backlog. We will work closely with Dr. Squire to realize this goal.

With regard to inadequate monitoring and management, we believe that reorganization of the program area has created a situation where scientists within the program can devote sufficient time to monitoring performance. The chemical selection process has been entirely changed; it now begins with interagency input provided by a subcommittee of the DHEW Committee to Coordinate Toxicology and Related Programs. This interagency subcommittee, with staff support from NCI contractors, undertakes to select chemicals for carcinogen bioassay and has available to it not only information for such purposes and an understanding of the laws and regulations that are entwined in this effort, but also the capability of directing that certain chemicals be prescreened using short-term tests. This is an innovation which we believe will enhance the efficiency of the selection process. Chemicals nominated for carcinogen bioassay will then be submitted to a public meeting of the National Clearinghouse on Environmental Carcinogens, which will serve, among others, two important purposes: 1) It will make public the intent to test specific chemicals, and

2) it will provide opportunity for public comment prior to final decision. The process of chemical selection cannot be arbitrary or capricious. We must be able to defend in rigorous scientific, public health, legal, and regulatory terms the basis for our selection. We believe that the Government committee will work closely and effectively with the Clearinghouse and that together they can ensure that we optimize the effectiveness and objectivity of the chemical selection process.

Regarding specific comment concerning inhalation guidelines, water treatment problems, etc., my comment here is, and it is consistent with the AMETA report, there was no clear division of responsibility between NCI staff and the Tracor Jitco prime contract. We are proceeding to change that now so that it becomes clear as to what their responsibilities are. In fact, there is considerable question whether it was appropriate to direct Tracor Jitco to develop inhalation guidelines or to carry out some of the other tasks that had been assigned to them. We must make the distinction between the science that involves concepts and innovation from the science that involves management, and be sure that the prime contractor is concerned with the latter not the former.

Regarding the AMETA report, we have met several times with AMETA personnel in an effort to implement procedures consistent with their recommendations. I can report that we have made progress in this area and I am confident we will persevere in efforts to create full accord between actual program management and that viewed as ideal on the part of the AMETA management team, to whom we owe great thanks.

It was pointed out that in hearings before the Subcommittees on Health and Administrative Practice and Procedure I made the statement that we frequently site visit laboratories and that these site visits include unannounced visits. It was my understanding that was also true of the bioassay program; it now is apparent I was misinformed. I do, however, know it to be true of many components of our programs, in other areas of the Division of Cancer Cause and Prevention as well as in the other Divisions. As pointed out above, steps have been and are being taken to correct the problem with respect to the bioassay activity.

I have already addressed, at considerable length, the modifications of previous contractual arrangements with the prime contractor. I believe we have made progress in this area, but will continue to make contract modifications consistent with our perception of the needs and requirements. I have every reason to believe that the past three months have been filled with activities which have not only resulted in actual improvements, but in a more important and yet less obvious way these activities have been a source of great education to our staff. I am confident they are, as a consequence, better able to deal with the complexities of contract management and interfacing research with management than was previously the case. It is my belief we have a cadre of dedicated, competent people working on the problems of bioassay who strongly sense that these are indeed exciting times and are committed to working together in the best interests of the program and the public health.

I appreciate the positive input from you and your staff and the impetus you have provided us in our efforts to combat the Nation's cancer problem.

Sincerely yours,

Rauscher

Frank J. Rauscher, Jr., Ph.D.
Director, National Cancer Program

Enclosure

AGENDA FOR HUNT VALLEY RETREAT - (August 23-24, 1976)

Chairman: Robert A. Squire, D.V.M., Ph.D.

1. Relationships between Tracor Jitco and NCI
   - a. Management Philosophies (NCI, T/J)
   - b. Mutual Expectations
   - c. Appraisal of Progress
   - d. Thoughts - Anticipation of the Future

2. Program Operation
   - a. Delineation of Areas of Responsibility
   - b. Communications between Staffs
   - c. Science Director and Tracor Organization
   - d. Revision of Information Systems
   - e. Award Fee Restructure
   - f. Revision of Mandatory Number of Chemicals Annually Placed on Bioassay
   - g. Separate Plan for Backlog
   - h. Other Comments Relative to the AMETA Report

3. Other Topics
   - a. Reduction in the Number of Unreported Chemicals (Philosophy, Schedule, Specific Plans)
   - b. Proposal Evaluation - Elimination of Poor Performers, New Respondees, Laboratories which Prefer Only 2 or 3 Chemicals, Overseas Laboratories.
   - c. Budgetary Limitations on Tracor Staff
   - d. Contract Delays

PARTICIPANTS

NCI	Tracor Jitco, Inc.
Mr. K. Born	Mr. G. Carr
Dr. T. Cameron	Mr. G. Maton
Dr. J. Douglas	Mr. D. Minnick
Dr. R. Squire	Dr. C. Wessel

Senator KENNEDY. In a number of extremely important instances the monitoring of these guidelines have just not worked.

I suppose, as one has indicated, this has been a very constructive step by the NIH in promulgating these guidelines. I mentioned in my opening statement they can be perfected, developed, changed, as knowledge of the art moves forward, and I am sure that will take place. I think we also have to note, however, that in area monitoring the record just has not been that good.

I am just wondering what you can tell us about your own attitude toward how the public, why the public is going to believe that it is going to be very much better in this area?

Dr. FREDRICKSON. I think, Mr. Chairman, that is a very important point that you have raised.

I have seen the correspondence from the committee and the reply of Dr. Rauscher relative to the work on bioassay of carcinogenic materials, not of course within the recombinant DNA area, but nevertheless important scientific work.

I think the question is most important relative to the matters before this committee.

I think, if I may say a word of preface, Mr. Chairman, that recombinant DNA is one exciting but rather narrow instance of new problems in laboratory safety which have arisen slowly as science has progressed and become more powerful, with the increasing recognition of a wide range of problems that now result from today's techniques.

This kind of research has been given a tremendous amount of attention by the NIH and by the community in general, and it has taught us a number of things.

My view on the use of these guidelines follows the following lines. I think it is very important to note that these guidelines can be easily referred to as voluntary. With respect to all those grantees and contractors who will be supported by NIH, the guidelines become obligatory. They place a great deal of emphasis on local responsibility.

The principal investigator is given a series of responsibilities which are clear and unavoidable, including the education and training of all of those who work with him with respect to all potential hazards. He is surrounded by the institutional biohazards review committee which must be in place, and which must sanction and certify the place of work.

He is then incapable in that surrounding of working in isolation, and in addition to that there are brought on these scientists, supported by NIH and similar agencies, a tremendous number of peer pressures, whose whole direction is toward forcing into the open, and into the sunshine, all of the practices and experiments which they have conducted.

There is, thus, a tremendous force that bears upon the experimentalist in this setting, which I think cannot be ignored, and which probably is more important than any other form of sanction or penalty that one might devise, for it involves ultimately withdrawal of his opportunity to do that work, withdrawal of the support.

Senator KENNEDY. I suppose the question is therefore what you obviously want is the least Federal overview necessary, but enough to make sure that there are going to be adequate protections—guidelines are one form, and regulations are a more significant form.

And finally, there is legislation. It is my own view that we want the least that is necessary, but we want to make sure that what is promulgated is going to be followed, and going to be enforced, and going to be oversight and evaluation.

I think what we have seen in terms of the past in our pursuit in terms of these areas—and they are extremely important—we have not seen this as a matter of priority by the Department, and in an area which is as sensitive as this, and as significant and as important, and we commend the promulgation of the regulations, but we are extremely chary of how really effective they are going to be, and what the willingness is going to be in terms of enforcement and overseeing these.

That is why I stress this, and want to indicate very clearly that this is going to be something that we want to work very closely with you on, and we will.

We want to make sure that there will be follow up and performance in this area.

Dr. FREDRICKSON. Yes, we regard that, of course, as extremely important, Mr. Chairman. It is essential that these guidelines be extended to the whole universe of activity of this kind in this country, and we hope consistent guidelines will be adopted throughout the world where much of this research is going on.

This, as my prepared testimony indicates, is to be the thrust of the interagency committee which has now been formed on the receipt of a letter from the President to the head of all the relevant departments and agencies who have an interest in either conducting or supporting this research, or whose statutory authority or regulatory activities may fall astride of it, and who have constituencies throughout the country.

Because nearly all of the Government agencies have come into compliance, we believe that one of the most important tasks now facing that committee is to work to determine how it best can be extended to the rest of society, American industry. The task is to consider then, and without delay, all of those measures that might be required to bear upon this matter of enforcement and compliance that you have described as being extremely important, for indeed it is that.

We are actually talking about two different populations to a certain extent, in regard to the pressures that play on academic scientists who engage in not for profit activities, and industry where there are other determinants of the degree of openness or opportunity for sharing.

Nevertheless, I think it should not be overlooked that industry has true capability in this field without question great expertise and equipment. I think in the main, from my experience meeting with industry in June, I see a real desire on the part of industry to organize itself in some kind of way to move toward voluntary adoption of these guidelines, and to use them effectively.

Senator KENNEDY. Do you think industry should follow these guidelines?

Dr. FREDRICKSON. Yes, I think industry should follow these guidelines. I think there are several problems within the guidelines that are relatively minor administrative matters which trouble industry, which they will undoubtedly raise with you.

Examples of such problems are the size of the batch (large for academic researchers, but tiny for industrial work), and some questions of how trade secrets and so forth can be protected, at the same time permitting enough exchange of information for the protection of all concerned.

Senator KENNEDY. Let me ask you, are you satisfied that you know the extent of the research that is being done by industry today?

Dr. FREDRICKSON. No. No, I think there is no compilation, no adequate registration of all the activity in the country today. I am not even satisfied that we know exactly what our NIH grantees are doing, because we have just recently implemented a point at which they must come into compliance with these guidelines, and we shall very shortly have that information in great detail. We have not had it before.

Senator KENNEDY. Is this not a rather ominous sign, that possibly this research is being now done in industry in various parts of this country and not complying with NIH guidelines?

Could that not be an ominous situation?

Dr. FREDRICKSON. Well, Mr. Chairman, although I cannot tell you from certain knowledge, it is very probable that the precautions being taken by industry, where it may be engaged in this, may be every bit as stringent——

Senator KENNEDY. You do not know that, though?

Dr. FREDRICKSON. I do not know that.

Senator KENNEDY. You cannot say it is or is not? It may be less, too?

Dr. FREDRICKSON. As I have indicated, I cannot say.

Senator KENNEDY. But do you not think it is extremely important that at least you have some kind of idea as to the extent of this kind of work or research that is being done by the industry, or just to know they are going to comply with this?

Dr. FREDRICKSON. Well, I think it is necessary to have more than just a statement that all groups involved will comply. I think it is essential that there be sufficient exchange of information so that our guidelines in general can be adopted——

Senator KENNEDY. You are not getting that information at the present time, are you?

Dr. FREDRICKSON. No, we are not at the present time. But, of course, it is the thrust of these guidelines to provide that implementation.

Senator KENNEDY. They are not covering industry, are they?

Dr. FREDRICKSON. We have not yet developed a mechanism for doing it.

Senator KENNEDY. That is the point, as I understand it. You do not know. They have not applied to industry. And yet the dangers, for all the reasons that you outlined here, as well as the opportunities for the implementation of these guidelines, as far as NIH, the same reasons apply as well for industry. And you say it is urgent for Agriculture, it seems to me to be urgent for industry as well.

Dr. FREDRICKSON. I think it is equally urgent for all of those who are conducting this research to come into common accord.

Senator KENNEDY. How are we going to get them to do it?

What steps are you taking now to get industry to comply?

Dr. FREDRICKSON. The interagency committee to which I referred earlier, which has now been set in place by the President's letter to all departments and agencies, has this contact as one of its three major tasks, and will attempt to deal with industry and its representatives to determine how best industry in general will be able to come into accord with these guidelines.

And on the basis of that experience, in part, the committee will make certain recommendations to the administration and the Congress, after it has observed as best it can what appears to be the nature of the problem.

Senator KENNEDY. Do you know all the companies or industries that are doing any research in recombinant DNA?

Dr. FREDRICKSON. I do not know all the companies.

Senator KENNEDY. Do you know some of them, what percent would you say, just a ballpark figure?

Dr. FREDRICKSON. I would make a ballpark estimate that there are not 20 in the United States doing significant recombinant DNA research, maybe fewer than that.

Senator KENNEDY. I know from my own experience, the enormous interest that this had in the community in Cambridge, Mass., when this was announced. They had close to a thousand people turn up at a city council meeting that wanted to know. It was active in terms of the local community leaders, as well as the scientists and researchers.

They had, I think, a valued exchange at that time. And they know that the research that is going to be done, or at least would be done under NIH contracts, are going to have the kind of protections which have been outlined by the NIH, which is a very, very important protection for them.

In these 20 other areas I wonder how many of the people in those communities know what is going on, when in many instances those industries either may or may not be having protections which are stringent, and tight as the NIH.

I would think they would have an important right to know. They will know very well if someone was going to put a jail down in the community, or a bar house, or a police station or a new plant, or factory, and they express their approval or disapproval about these matters.

It seems to me that they have a right to know these issues, do you not think so?

Dr. FREDRICKSON. Mr. Chairman, I think it is essential that the public make such inquiries as you have referred to. I think it is extremely important that the public be informed, and I think that will be the case more and more, as we deal with problems that lie beyond recombinant DNA research.

Senator KENNEDY. What kind of chance do they have now? I suppose from your own knowledge you can tell them some of the areas around the country where some of these companies are going ahead. But from GE we do not know. We asked them to come here, and not to get into the details of the specifics, obviously trade secrets, but to try to find out what is happening, what is going on in this one industry, and we could not.

How are they going to know? How are people in a particular community going to know whether that company is doing it or not?

How are they going to find that out?

Dr. FREDRICKSON. I think part of the answer to that question will lie with industry's ability to respond to the need, and to the importance attached to the awareness of the community with regard to the activities of an industry within it.

Senator KENNEDY. Who is going to do that now? Who is going to find out whether industry is or is not going to do it?

That is not the function and purpose for us to try to find out every industry and haul them all up here and say are you or are you not going to do this kind of thing.

Obviously, the public interest, the consumer interest, is significant in this area. Who is taking the responsibility?

We want to find out whether you see it as your responsibility, and then if you do not, are we going to take it as sufficiently important that we do?

We want to hear obviously from the science community to see whether we should or should not, or what the nature of this is.

Who is going to take it?

You do not see it as your responsibility to know the extent that this is being done in industry, and what kind of protections are being implemented by various industries to protect the public, do I understand that?

Dr. FREDRICKSON. It is, of course, in our interest to know what is going on in industry, and to make sure that if we do not find it out, someone else does. Because all of us are involved in the protection of access to these important techniques, and their use with the greatest care for the public good.

This matter is precisely what the Interagency Committee, to which I had earlier reference, intends to deal with. It will examine the statutory authority that now exists for CDC, for OSHA, and for certain other of the regulatory agencies, and attempt to draw conclusions and recommendations for possible change, if that be necessary.

Certainly, in the first instance it behooves industry to organize itself to make every attempt to respond to this need that you have outlined.

Senator KENNEDY. I could not agree with you more. I was just trying to think if they do it, fine, if they do not, what the next step is, and how do we find out who is doing it.

I agree with you, if they conform, comply. You yourself have said you do not know which industries are doing it.

We do not know which industries are doing it. It would be nice if every one of them said we are doing it, and we are going to conform or comply with it. But we do not know that. It is being done today, and there are people in those communities that do not even know.

I am not trying to dramatize the importance within the community, because we all know it reaches far beyond it. But that is the nature of the particular dilemma, and I think we ought to have a great sense of urgency.

I am sure you believe that.

When will your agency report come back to us with a recommendation as to what will be done in terms of industry, and what you feel can be done in terms of your various legislative authority and power, and what you are going to recommend to us in terms of any legislative authority as well?

When can we expect that?

Dr. FREDRICKSON. We have yet to have the first meeting of this newly established Interagency Committee. That will occur in October. I should hope that we would strive before December to reach some conclusions that will be of value in regard to these matters.

We will certainly press on with urgency in this matter.

Senator KENNEDY. What is the date in October?

Dr. FREDRICKSON. We have not yet set the date, sir.

Senator KENNEDY. What sense of urgency can we gather about this?

How can I go to the industry people and say we are really concerned about this, when the Government Interagency Committee has not set a date on it?

How do I say the thing is really important? They will say you have got an Interagency Task Force that is not even setting a date, so why are you getting so excited, Senator.

What do I tell them?

Dr. FREDRICKSON. Mr. Chairman, we have already alerted industry, and we have alerted all Government agencies, in June and April respectively, to what we consider the urgency of this matter, the requirement that they inform themselves, and their need to organize to respond to some of the considerations you have described.

It is not the first time then that both sectors have been aware of these problems, as well as the concern that has come to us from a variety of public commentators about the questions of compliance, regulation and enforcement.

Senator KENNEDY. The first interagency meeting I understand was April 8.

Senator Javits and myself wrote on July 20, trying to get action in these agencies. We have not gotten a letter back. We hear about an additional meeting in October, a date which has not been established yet, and that is basically 5 months ago, when your other meeting was.

I know we all have enormous areas of responsibility, and are busy, but I think if this has the potential that it does have, which you have testified to, we have to get a greater sense of urgency about it.

Senator Schweiker?

Senator SCHWEIKER. Thank you, Mr. Chairman.

Dr. Fredrickson, in your statement on page 4, you say, "a special meeting of the Advisory Committee to the Director, NIH, was convened in February of this year to review these proposed guidelines."

Does this group include any representatives from the Defense Department at all?

Dr. FREDRICKSON. No, that group did not. I believe you are referring to the Director's Advisory Committee, the meeting held in February.

Senator SCHWEIKER. On page 7 you say:

> It should be noted that the National Science Board has adopted by resolution the NIH guidelines for all such research supported by the National Science Foundation. We anticipate similar letters of endorsement from all of the Federal agencies that are now conducting or supporting such research, or consider that they may do so in the near future.

Do you include any element of the Defense Department in this statement?

Dr. FREDRICKSON. Yes.

We have received a communication from the Defense Department indicating that it is not now conducting research of this kind and that should it do so, it would adopt completely the NIH guidelines.

Senator SCHWEIKER. It did agree. All right.

Does this include CIA?

Dr. FREDRICKSON. It does not include the CIA, at least in matters of reference to that letter.

Senator SCHWEIKER. How about the CIA using a cover, perhaps in one of the Government agencies, to do this sort of research?

I am thinking of the shellfish toxin case, when our Select Committee on Intelligence learned that the CIA used the Public Health Service as a cover to conduct research on shellfish toxin, and funded it through the CIA secretly.

My question to you is, if the CIA were to use one of these agencies as a cover for CIA research, do the guidelines apply, and are you knowledgeable about it?

Dr. FREDRICKSON. I am not knowledgeable about any such activities on the part of the CIA, and I cannot anwser your question about reference to the guidelines.

But I feel certain that all Government agencies will shortly be under these guidelines.

I think that will be the first action of the committee which we have been discussing.

Senator SCHWEIKER. You include the CIA in that statement then?

Dr. FREDRICKSON. We will attempt through the administration to be sure that the CIA is informed and to get such a response, yes.

Senator SCHWEIKER. Since that is the one element of secret funding throughout Government, it seems that it is probably the most important element that we are talking about because, obviously, if it is secret, we would not know about it, and maybe you would not know about it.

It seems to me that your responsibility here ultimately should include dealing with this question of possible CIA research.

I realize we have passed a bill here in the Senate that has not yet cleared the House, which would give your group authority in this area.

But, lacking passage of that bill, I would still hope that you would accept some responsibility here because of what has happened in the past.

Dr. FREDRICKSON. We will certainly see that those concerns are carried to the administration, Senator.

Senator KENNEDY. We are impressed by your sense of urgency, Doctor, and the work that you have done. It is really up to the President. He can get the industries and he can get the governmental agencies. He has the power of the Executive order to do that. We understand that. And he can get the industries to move ahead.

I think we just want him to feel the sense of urgency and the importance of this that obviously you do.

I think we understand on this side of the table what the realities of this is. If he believes it is important, we ought to get about the business of it.

Dr. FREDRICKSON. If I could add one final comment in that regard.

I completely agree with you, of course. One reason for the apparent deliberateness of this series of moves, however, is the fact that these guidelines were published for comment on June 23, and the draft environmental impact statement only the first part of this month. Adoption of these guidelines depends somewhat on the form they take after comment has brought some final revision. Therefore, we wanted the agencies to consider carefully during this process of development of the guidelines how they can and will adopt these guidelines, because I think a certain amount of deliberateness without procrastination is required.

Senator KENNEDY. Could you go briefly to page 9 concerning patent policy review?

Dr. Fredrickson. Here I have reference in my prepared statement, Mr. Chairman, to a review which is underway of the Department patent policies as they relate to discoveries in recombinant DNA research. A number of universities where such research is being conducted are reviewing possible patent applications for these discoveries.

Stanford University and the University of California have filed patent claims in this research area and have solicited the views of the Department and the NIH. These patent activities, the certitude that other important inventions in the field are forthcoming, and the public's apprehension over control of recombinant DNA research, compel inquiry into whether the Department's policies for allocating invention rights are consonant with the concerns about this research.

Invention rights are normally allocated in either of two ways under current Department patent regulations: The Department has institutional patent agreements with 65 universities which have identified technology transfer capabilities. Such an agreement provides the institution the first option to ownership in all inventions made in performance of Department research, subject to a number of conditions deemed necessary to protect the public interest. Stanford and the University of California are among the institutions that hold such agreements with the Department.

Second, for those institutions which do not have an institutional patent agreement, the Department defers determination of ownership until an invention has been made.

Senator Kennedy. Would the patent given the inventor, would there be control over the safety guidelines, to loosen them or tighten them——

Dr. Fredrickson. The holding of the patent by the inventor permits him to establish certain conditions for the issuance of licenses, either exclusive or nonexclusive. The holders of such patents could insist that licenses would only be granted on the conditions the guidelines were followed.

Senator Kennedy. If you are going to permit a university to be able to alter or change those by the policy, it seems to me a rather significant deviation of the existing guidelines.

If they are going to be able to be altered or changed, should they not be done generally?

If a particular university has knowledge and awareness, should they not be done generally?

Dr. Fredrickson. No, Mr. Chairman, you are under a misapprehension.

The holder of the patent could not change NIH guidelines with reference to the use of a license.

Senator Kennedy. Can they alter or change the conditions under which the research is done?

Dr. Fredrickson. They presumably can. Each of these would be a matter to be separately determined. Certainly we regard it as possible for the holder of such a patent to insist that the guidelines be followed. I think certainly they cannot alter the guidelines.

Senator Kennedy. They can alter, can they not, significantly the research that is being conducted in terms of the safety guidelines?

Would that be left to the universities themselves under patent agreements?

Dr. Fredrickson. No. They cannot alter those safety arrangement agreements.

Senator Kennedy. All research being done under patents must comply with the guidelines?

Dr. Fredrickson. If that is the condition posed, yes.

Senator Kennedy. What do you mean?

Why is it not all? Why is it not for all of them?

Dr. Fredrickson. Mr. Chairman, if it is a condition for all such activity in the United States, yes, the guidelines will apply.

Senator Kennedy. Will it not be?

Dr. Fredrickson. We are now reviewing this process as to what condition we shall apply for DNA recombinant research under these institutional patent agreements.

One of the options we are considering is that we would allow the inventor to hold the patent, but that as a condition for licensing any other user the guidelines must be followed. This would be in advance of and before universal extension of such guidelines to all who might conceivably use the invention.

Senator Kennedy. I am not sure whether we have the assurances that if patents are let, that we have the absolute assurances that in all circumstances the guidelines will be followed. And whether you are reserving to yourself the ability in the patent area of making adjustments or changes in terms of the guidelines.

Dr. Fredrickson. Well, I have not yet made a final determination. I am receiving a wide variety of comments, and certainly welcome this opportunity to bring this to your attention.

Senator Kennedy. Can you let us know if you are going to vary or change that?

Dr. Frederickson. I most certainly will see that you are informed before that policy is promulgated.

[The prepared statement of Dr. Fredrickson follows:]

FOR RELEASE UPON DELIVERY

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

STATEMENT BY

DR. DONALD S. FREDRICKSON, DIRECTOR

NATIONAL INSTITUTES OF HEALTH

ON RECOMBINANT DNA RESEARCH

BEFORE THE

SUBCOMMITTEE ON HEALTH

SENATE COMMITTEE ON LABOR AND PUBLIC WELFARE

SEPTEMBER 22, 1976

Mr. Chairman and Members of the Subcommittee:

It is a pleasure to appear before you today to discuss the NIH guidelines on recombinant DNA research.

In June, the National Institutes of Health, with the approval of the Secretary of HEW and the Assistant Secretary for Health, issued guidelines to govern NIH-supported research on recombinant DNA molecules. Accompanying the guidelines was a document describing in detail the issues which the Director of NIH considered in reaching the decision to release the guidelines. These guidelines, governing research conducted at the laboratories of NIH as well as projects supported by grants and contracts, delineate stringent safeguards for the conduct of experiments involving the production of recombinant DNA molecules and their insertion into organisms such as bacteria. The object of the guidelines is to minimize the risks associated with recombinant DNA research--primarily through a series of procedures aimed at physical and biological containment of possibly dangerous organisms--while permitting research of great potential benefit to mankind. The NIH guidelines replaced the recommendations from the 1975 Asilomar Conference on Recombinant DNA Molecules, which permitted research under less strict conditions.

Recombinant DNA molecules are formed in the laboratory from recombination of segments of deoxyribonucleic acid, the material that determines the hereditary characteristics of all living cells. These techniques, permitting genetic information from quite different organisms to be combined, have a remarkable potential for furthering the understanding of fundamental biochemical processes of both lower and higher organisms.

Recombinant DNA research has strong potential in medicine as well as in science and technology generally. In medicine it is capable of providing hitherto unobtainable knowledge of the organization and expression of genes in health and disease. It possibly may also permit economical production of important medicinals. Potential benefits in agriculture and industry include more abundant crops and synthesis of industrially important biochemical agents such as enzymes.

There are risks, however, as well as potential benefits in the new research. For example, bacteria with transplanted genes may prove hazardous to man or other forms of life. Like many of the potential benefits, these risks remain speculative, for there is still scanty evidence that genes from one form of life can be expressed in any other form. We must assume, however, that they may be. Thus our present state of knowledge dictates strict controls on this form of experimentation.

The NIH guidelines prohibit certain types of experiments--those, for instance, that might produce disease germs with increased resistance to antibiotics. Other experiments will go forward under special safety conditions. The guidelines have a definitive administrative framework for assuring that safety is an essential and integrated component of research involving recombinant DNA molecules. The section dealing with roles and responsibilities sets forth a developed review structure involving the principal investigator, local biohazards committees, and the NIH Advisory Committee, as well as peer review committees. The guidelines now provide extensive opportunity for advice, from the local to the national level. Several levels of review and scrutiny are provided, ensuring the highest standards for scientific merit and conditions for safety. We believe these provisions will afford protection, and with a wide margin of safety, to workers and the environment while permitting this type of research to proceed. And the NIH is sponsoring additional experimental work to determine possible hazards and new safety practices and procedures.

Development of the Guidelines

Recombinant DNA research brings to the fore certain problems in assessing the potential impact of basic science on society as a whole, including the manner of providing public participation in those assessments. The field of research involved is at the leading edge of biological science. New information is accruing rapidly and requires continuing evaluation and re-synthesis. The experiments involved are extremely technical and complex. Molecular biologists active in this research require diligence to keep abreast of the newest developments. It is not surprising that scientists in other fields and the general public have difficulty in understanding advances in recombinant DNA research. Yet public awareness and understanding of this line of investigation is vital.

It was the scientists engaged in recombinant DNA research who called for a moratorium on certain kinds of experiments in order to assess the risks and devise appropriate guidelines. At their behest, the National Academy of Sciences created a committee that organized an international conference at Asilomar Conference Center in California, held February 1975. The committee also called on the NIH to establish an advisory committee to draft guidelines for the conduct of this research. At Asilomar, temporary guidelines were issued pending issuance of NIH guidelines.

In response, the NIH Recombinant Advisory Committee (formally "NIH Recombinant DNA Molecule Program Advisory Committee") was established in October 1974 to advise the Secretary of HEW, the Assistant Secretary for Health, and the Director of NIH to accomplish these tasks. The several meetings at which the Recombinant Advisory Committee developed its proposed guidelines in 1975 were announced in the Federal Register and were open to the public. The committee, after working several draft versions, reached agreement on a recommended revised version of proposed guidelines that were referred to the NIH Director for review in January 1975.

A special meeting of the Advisory Committee to the Director, NIH, was convened in February of this year to review these proposed guidelines. In addition to current members of the committee, a number of former committee members as well as other scientific and public representatives were invited to participate in the special February session. There was ample opportunity for comment and an airing of the issues, not only by the committee members but by public witnesses as well. All major points of view were broadly represented.

The proposed guidelines were reviewed in the light of the comments and suggestions made by the participants at the public hearing as well as extensive written correspondence received after the meeting. The NIH has published a volume containing the transcript of the public hearing of the Director's Advisory Committee, all correspondence directed to the NIH on this matter, and summaries of meetings with representatives from Government, Departments, and Agencies, Congressional staff, and industry. The Decision of the Director, NIH, that accompanied the release of the guidelines in June is based on that record.

Steps are underway for further opportunity for debate, scrutiny, and subsequent decisions relevant to the guidelines. The guidelines were published in the Federal Register on July 7, and a 120 days' period was allowed for comment. Further, in response to the recommendations of public commentators, the NIH undertook an environmental impact assessment in accordance with the National Environmental Policy Act of 1969. A draft environmental impact statement was published in the Federal Register on Thursday, September 9, 1976, for public comment. The statement was given widespread distribution to interested environmental Federal, State, and local groups for comment. In this way, yet another review will be provided from the perspective of the environmental impact of this research.

Application to Public and Private Sector

The Department and NIH have given high priority to the implementation of the NIH guidelines and their application beyond the NIH. A meeting was held with representatives of relevant HEW agencies and other departments of the Federal Government on April 8. The purpose was to exchange information on recombinant DNA research and to discuss the applicability of NIH guidelines to research or regulatory activities of other departments and agencies.

A meeting was also held on June 2 with representatives of private industry to provide them with full information about the guidelines and to help determine the present and future interest of industrial laboratories in this type of research. The meeting afforded one of the first opportunities for industry representatives to convene for discussion of this research.

The expressed concern for the extension of these guidelines to other Federal agencies and the private sector is shared by the NIH and the Department of Health, Education, and Welfare. The letter from you, Mr. Chairman, and Senator Javits to the President expressed well these timely concerns. Following the NIH initiatives, the Department has been reviewing an appropriate mechanism to allow for a policy review of Government activities in this research area, including relevant activities in the private sector. The Department has proposed to the President that an interagency committee be created to review the activities of all Government agencies conducting or supporting recombinant DNA research or having regulatory authority relevant to this scientific field. This committee could also coordinate activities with the private sector. The President has written to relevant Department Secretaries and Agency Heads urging their cooperation and participation in naming representatives to serve on this committee.

The interagency committee will assist in facilitating compliance with a uniform set of guidelines for the public and private sectors and provide coordination among the several Government agencies that support or conduct this research. It is mandated to suggest appropriate administrative or legislative proposals deemed appropriate for national implementation. For this purpose a review of authorities--the Public Health Service Act, the Occupational Safety and Health Act, the National Environmental Policy Act, and other relevant statutes--will be carried out.

It should be noted that the National Science Board has adopted by resolution the NIH guidelines for all such research supported by the National Science Foundation. We anticipate similar letters of endorsement from all of the Federal agencies that are now conducting or supporting such research, or consider that they may do so in the near future.

Since the NIH meeting with private industry in June and following publication of the NIH guidelines in the Federal Register, the Pharmaceutical Manufacturers Association has been reviewing the applicability of the guidelines to industry research activities. The PMA has expressed general support for the guidelines with relatively minor revisions considered necessary to meet the needs of industry.

In order to ensure that implementation of the guidelines within the NIH be achieved without delay, an NIH Office of Recombinant DNA Activities was created in June to administer and coordinate activities. This office will serve as liaison to the institutional biohazard committees for administration of the guidelines. There will be special emphasis on activities pertaining to the operation and implementation of containment and safety practices and procedures. The NIH office will also closely monitor reports and information concerning accidents, containment, and safety research innovation.

To ensure that those who conduct recombinant DNA research will have notice and adhere to the guidelines, the NIH distributed the guidelines to approximately 25,000 grantees and contractors. The investigators and institutions supported by the NIH have a special responsibility for maintaining the safety practices outlined in the guidelines, and the NIH will work closely with them to fulfill that objective.

In response to public concern that broad support for the guidelines be solicited, the NIH undertook to distribute them through a number of channels. Letters were sent to professional organizations soliciting support for the guidelines among their member scientists and to editors of journals requesting editorial endorsement. The guidelines were also sent to all science attaches of foreign embassies located in Washington and to U.S. science attaches in our embassies in foreign countries. Various international health and scientific organizations have also been briefed on the guidelines.

The NIH recognizes its responsibility to continuing discussions on the international level to ensure that there be as uniform a standard of guidelines as possible to govern the conduct of this research in all nations. As an example of international cooperation, the European Molecular Biology Organization recently announced plans for a voluntary registry of recombinant DNA research in Europe. Following this EMBO initiative, NIH shall similarly maintain a voluntary registry of investigators and institutions engaged in such research in the United States. Plans for establishing this registry are under way, and the new interagency committee will be asked to address the scope of the registry as one of its earliest tasks. Great Britain has endorsed continuation of recombinant DNA research, and a Government report has just been issued containing guidelines that technically are similar to the NIH guidelines.

Patent Policy Review

Currently there is also a review underway of the Department patent policies as they relate to discoveries in recombinant DNA research. A number of universities where such research is being conducted are reviewing possible patent applications for these discoveries. Stanford University and the University of California have filed patent claims in this research area and have solicited the views of the Department and the NIH. These patent activities, the certitude that other important inventions in this field are forthcoming, and the public's apprehension over control of recombinant DNA research compel inquiry into whether the Department's policies for allocating invention rights are consonant with the concerns about this research.

Invention rights are normally allocated in either of two ways under current Department patent regulations:

The Department has institutional patent agreements with 65 universities having identified technology transfer capabilities. Such an agreement provides the institution the first option to ownership in all inventions made in performance of Department research, subject to a number of conditions deemed necessary to protect the public interest. Stanford and the University of California are among the institutions that hold such agreements with the Department.

Second, for those institutions who do not have an institutional patent agreement, the Department defers determination of ownership until an invention has been made. Under the deferred determination policy, an innovating institution may petition the Department for ownership of an invention after it is identified. In the past, approximately 90 percent of all such petitions have been granted.

The Department's policy of allocating invention rights is designed to facilitate the transfer of technology from the bench to the marketplace by inducing industrial investment and continued development of inventions generated with Department support. The incentives provided by Department patent policy have encouraged the development of new technology in general and afforded patent protection for some inventions to the economic benefit of the United States. The control of DNA research envisioned by the guidelines, however, requires a delicate balance between need for rapid exchange of information and a potential means for achieving greater uniformity in safety practices by setting conditions for safety in licenses under patent agreements.

Stanford and the University of California have indicated a willingness to consider modification of their patent agreement with the Department as it relates to such research. A number of possible policies, short of the present allocation of rights under the agreement, are currently being considered by the NIH as possible alternatives to the present allocation of rights made under all such agreements. As part of that review, the NIH has solicited the views not only of members of the NIH community but of the public as well, including all those who participated in the public hearing on the guidelines.

The prudence and caution inherent in the guidelines must also be reflected in patent policies underlying administration of recombinant DNA research inventions.

Conclusion

In summary, the potential benefits and risks of recombinant DNA research have posed a singular challenge. The prospects of harnessing these techniques to the benefit of man are indeed great. From what we know today, we must assume that if these promises are to be realized, our efforts must be marked by extraordinary diligence to avoid harm. This combination of benefits and risks provides not only opportunity but obligation for the scientific community and the public to proceed together in assessment of risks and benefits and to agree upon procedures that will allow the continuation of these investigations under conditions of minimal risk.

Our immediate task is threefold: First, to maintain a satisfactory process for updating and revising the guidelines in the light of both public scrutiny and new research developments. Secondly, to pursue steps to ensure that all sectors of the scientific enterprise in this country concur and adopt these or comparable guidelines, and to use all influence available to us to encourage a consistent policy throughout the world. Thirdly, we must now, in concert with all interested parties, consider whether additional measures to assure a common approach to problems here are advisable. Let me assure the Committee that the

Department will make every effort to accomplish these tasks.

Thank you for the opportunity to discuss these issues before the Committee. My colleagues and I would be happy to try to answer questions you or other members may have.

Senator KENNEDY. Thank you. Dr. Talley.

Dr. TALLEY. Mr. Chairman and Senator Schweiker, I wish to thank you for the opportunity to comment on the important emerging issue of recombinant DNA research.

The Environmental Protection Agency believes that the benefits and risks of recombinant DNA research are highly speculative at this time. As the agency responsible for environmental protection, however, we are concerned with the possible release into the environment of micro-organisms that might cause disease or adversely affect the environment.

Although the risks of recombinant DNA research appear to be low, the consequences of an untoward event could be catastrophic. Prudence dictates that we proceed with extreme caution in this area of research.

I would like to applaud the scientific community for its efforts over the last 2 years to carefully examine the possible hazards of recombinant DNA research, and to seek ways in which to minimize any dangers.

I also applaud the leadership of the National Institutes of Health for the development of guidelines for the safe conduct of such research. The NIH guidelines appear to be a reasonable initial step for minimizing the risks to laboratory workers and the environment while permitting recombinant DNA research to proceed. Any such research should be closely monitored by NIH and the scientific community to assure that the guidelines are adequate to provide continuing protection.

There should also be continuing research on the physical and biological controls of recombinant DNA research so as to increase the margin of safety against potential hazards.

Specifically, we believe taht recombinant DNA research should be performed on organisms which would be unable to live outside the laboratory environment and which are less ubiquitous than E. coli.

Strictest adherence to the guidelines will be necessary to protect workers and the environment from potential hazards. I support vigorous enforcement of the guidelines by NIH and urge the complete cooperation of the scientific community in implementing the guidelines.

Because the NIH guidelines only apply to research conducted or sponsored by NIH, universal protection against the potential hazards of this research can only be accomplished if the guidelines are extended to cover recombinant DNA research performed by other Federal agencies and the private sector.

I strongly support the extension of coverage of the guidelines to all recombinant DNA research performed in the Uinted States.

To this end, EPA will actively participate on the interagency committee on DNA research which has been established by the President.

I assure you that EPA will do all it can to help minimize the risks to the environment of recombinant DNA research.

This concludes my prepared remarks, and I will be happy to answer any questions you might have.

Senator KENNEDY. Do you think that just having guidelines is sufficient protection at this time?

Dr. TALLEY. If they are adhered to, at present I believe so.

Senator KENNEDY. I wonder whether just promulgation of guidelines is going to do the job.

Can you tell us about the E. coli?

Are you cocnerned about it weakening coli or what?

Dr. TALLEY. I think I should turn this discussion over to Dr. Frederickson.

We were talking about it before the testimony began.

Our concern is that despite the fact that the strains of E. coli that were used have been outside human beings for decades, and in terms of their lifetimes, it would be a millenia for us, there might be an added element of safety if the bacteria used were those that could not possibly survive outside the laboratory, let alone the human system.

Senator KENNEDY. E. coli lives in man, does it not?

Dr. TALLEY. Yes, sir.

Senator KENNEDY. You want to do it or it is safe to use one that does not live in a human being, is that correct, do you think it is?

Dr. TALLEY. If it would be possible to select bacteria that not only does not live in man, but could not survive in the general environment—the difficulty with that is that E. coli does represent the bacteria in which the greatest body of knowledge presently exists.

Senator KENNEDY. Thank you very much.

Dr. TALLEY. Thank you.

[The prepared statement of Dr. Talley follows:]

STATEMENT OF
DR. WILSON K. TALLEY
ASSISTANT ADMINISTRATOR FOR RESEARCH AND DEVELOPMENT
ENVIRONMENTAL PROTECTION AGENCY
BEFORE THE
SUBCOMMITTEE ON HEALTH
COMMITTEE ON LABOR AND PUBLIC WELFARE
UNITED STATES SENATE
SEPTEMBER 22, 1976

Mr. Chairman and Members of the Subcommittee, I am Dr. Wilson K. Talley, Assistant Administrator for Research and Development of the Environmental Protection Agency. I wish to thank you for the opportunity to comment on the important emerging issue of recombinant DNA research.

The Environmental Protection Agency believes that both the benefits and risks of recombinant DNA research are highly speculative at this time. As the Agency responsible for environmental protection, however, we are concerned with the possible release into the environment of microorganisms that might cause disease or adversely affect the environment. Although the risks of recombinant DNA research appear to be low, the consequences of an untoward event could be catastrophic. Prudence dictates that we proceed with extreme caution in this area of research.

I applaud the scientific community for its efforts over the last two years to carefully examine the possible hazards of recombinant DNA research and to seek ways in which to minimize any dangers. I also applaud the National Institutes of Health (NIH) for the development of guidelines for the safe conduct of such research. The NIH guidelines appear to be a reasonable initial step for minimizing the risks to laboratory workers and the environment while permitting recombinant DNA research to proceed. The research should be closely monitored by NIH and the scientific community to ensure that the guidelines are adequate to provide continuing protection. There should also be continuing research on the physical and biological controls of recombinant DNA research so as to increase the margin of safety against potential hazards. We believe that recombinant DNA research should be performed on organisms which would be unable to live outside the laboratory environment and which are less ubiquitous than E. coli.

Strictest adherence to the guidelines will be necessary to protect workers and the environment from potential hazards. I support vigorous enforcement of the guidelines by NIH and urge the complete cooperation of the scientific community in implementing the guidelines.

Because the NIH guidelines only apply to research conducted or sponsored by NIH, universal protection against the potential hazards of this research can only be accomplished if the guidelines are extended to cover recombinant DNA research performed by other Federal agencies and the private sector. I strongly support the extension of coverage of the guidelines to all recombinant DNA research performed in the U.S. To this end, EPA will actively participate on the interagency committee on DNA research which has been established by the President.

I assure you that EPA will do all it can to help minimize the risks to the environment of recombinant DNA research. This concludes my prepared remarks and I will be happy to answer any questions you might have.

Senator Kennedy. Our next panel of witnesses is made up of eminently distinguished scientists who have been active in this field and who will share with us some of their views and experience.

Dr. David Baltimore, Massachusetts Institute of Technology; Dr. Norton Zinder, Rockefeller University; Dr. Robert Sinsheimer, California Institute of Technology; and Dr. Halsted Holman, Stanford University.

I want to welcome all of you to the panel.

I think, in terms of both our own edification and benefit of the record it would be helpful if we could first have a brief comment and summation of different positions on this, and then if we could really talk and have each of you give your views about the importance and value of the guidelines. We should also discuss the public policy kind of considerations, whether communities ought to be notified or whether they should not be.

We would like to really keep it informal in the sense of being able to interact with each other's viewpoints. I think it would make the best record.

Dr. Baltimore, we want to welcome you to the committee.

I remember very well, as with other members of the panel, the interesting exchanges that we had down in Virginia at Airlie House.

We look forward to your testimony here today.

STATEMENT OF DAVID BALTIMORE, PH. D., MASSACHUSETTS INSTITUTE OF TECHNOLOGY; ACCOMPANIED BY NORTON D. ZINDER, PH. D., ROCKEFELLER UNIVERSITY; ROBERT SINSHEIMER, CALIFORNIA INSTITUTE OF TECHNOLOGY; AND HALSTED HOLMAN, M.D., STANFORD UNIVERSITY, A PANEL

Dr. Baltimore. My name is David Baltimore. I am an American Cancer Society professor of microbiology, Massachusetts Institute of Technology, 1975 Nobel Laureate in Medicine.

I was a member of the National Academy of Sciences committee that met in April 1974, and drafted the call for a delay in recombinant DNA research, which appeared in July 1974.

I was on the organizing committee for Asilomar meeting in February 1975, and have maintained an active involvement in attempts to regulate recombinant DNA research since that time.

Contemporary research in basic biology has been more productive of knowledge about living systems than of information useful in the treatment of disease. The lack of practical advances stems from the complexity of the problems; the available techniques can be used on bacteria but not readily on higher organisms.

Recombinant DNA technology has the potential to make modern biology more relevant to the problems of human disease. This new way of studying genes simplifies complex biological problems so their individual parts can be analyzed. A deeper understanding of how the systems in human beings function is sure to come from these new methods.

From this new understanding, novel methods are likely to evolve for preventing and treating the presently unconquered diseases that afflict us. Recombinant DNA research is our best hope for understanding diseases like cancer, heart disease, and malfunctions of the immune system, for which the prospects are poor for prevention solely by public health measures.

When the possibility of recombinant DNA research first appeared on the scientific horizon, the community of molecular biologists became concerned that there might be hazards in the work. This concern was rapidly transmitted to the public. Over the last 3 years, many biologists have participated in the unprecedented examination of how recombinant DNA work should be regulated, a process that involved them in assessing the magnitude of the risk.

To most biologists the risk appears small and controllable, but nonetheless they have concluded that stringent regulation is worthwhile until precise knowledge is available. Hopefully, such knowledge could allow the lowering of barriers to unfettered research.

The NIH guidelines provide stringent procedures for the conduct of recombinant DNA research.

While I would hope that in the future the guidelines might be proved overly restrictive, at present they seem to be an appropriate framework for allowing recombinant DNA research to go forward.

As presently formulated, the guidelines apply only to research funded by NIH. For work to proceed with maximum safety, the guidelines should apply to all recombinant DNA research, whatever its source of funds. It is especially important that nonacademic laboratories be covered.

Senator KENNEDY. Why?

Dr. BALTIMORE. I think for the reason you brought out so well in your discussion with Dr. Fredrickson. We in general know so much less about what is happening in industrial situations than we do in academic situations that it becomes even more important that there be stringent procedure for regulation. In fact, I can well imagine that there might be necessity for different types of monitoring of regulations in industry as compared to an academic situation because the academic situation has built into it a self-monitoring procedure.

Senator KENNEDY. Does the fact that no one knows how much is going on in industry and what protections are being applied by various industries, does that make you uneasy?

Dr. BALTIMORE. Yes.

I should imagine that if industry wanted to show that it was following the guideline, that would not be very difficult. They could invite panels of people to visit the laboratories. They could bend over backward in many ways to demonstrate that they are following the guidelines.

I fully feel from the small contact that I have had with industry that they, in fact, will try very hard to follow the guidelines because it is in their interest as well as ours.

Senator KENNEDY. But the fact that we do not know what is happening——

Dr. BALTIMORE. That is the most worrisome part.

Senator KENNEDY (continuing). Is a matter of concern to you?

Dr. BALTIMORE. Yes.

Senator KENNEDY. First, let me ask you specifically, do you think that the people in the communities where you work, in the Cambridge area, who are concerned with that, may be in greater danger from research being done among industry where they may not be following the guidelines.

Dr. BALTIMORE. I think it is very important that the local people educate themselves about what is happening in their local area. I agree completely that the danger to them is on a national level. It is by no means on a local level.

If, in fact, there is a hazard in recombinant DNA research, that hazard knows no boundaries of States or cities or towns.

Senator KENNEDY. In terms of potential danger do you mean really what might be happening out in California to people, even within a university setting where this research might be done, following these guidelines, it may be of greater potential danger to them—maybe?

Dr. BALTIMORE. Yes.

Senator KENNEDY. You do not know?

Dr. BALTIMORE. I say if there is a danger——

Senator KENNEDY. If I understand your position, where this kind of research is being done, they ought to be notified, should they not, and they ought to be aware of what is being done and ought to be at least able to discuss what is being done?

Dr. BALTIMORE. They certainly ought to be able to discuss what is being done.

Senator KENNEDY. And know what the protections are?

Dr. BALTIMORE. If they have shown an interest in being informed, they should definitely be informed in a very open manner.

I think scientists should make themselves as available as possible to respond to specific requests for information and for discussion with the public. If I described everything that went on at MIT to the local community, I think I would bore them very rapidly. I would not know what it is they wanted to know.

But, taking our lead from the newspapers and political leaders it is possible to respond to public concerns in a useful manner.

Senator KENNEDY. Well, let me put it in very graphic terms, about a little bug crawling out of a laboratory——

Dr. BALTIMORE. That hits the newspapers, and immediately the Cambridge City Council wants to know, and at that point it is our responsibility to tell them everything they want to know and be candid with them.

Senator KENNEDY. The public ought to know about this whole issue, should they not?

It just is not in the areas where they are considering locating research or a contract, but really the public ought to know because it may very well affect all of our lives?

Dr. BALTIMORE. I can only agree.

I did want to continue on one specific point, which is not in my formal testimony.

The relevance of advances in modern biology to problems of human health has been questioned repeatedly. I think this is a problem of seeing the future in terms of the past—the September 2, 1976, issue of the New England Journal of Medicine is, I think, a better guide to the future. One article there describes the use of a substance called interferon to treat the very serious disease of human hepatitis.

A million people in the world are chronic sufferers from this disease, including more than 1 per 1,000 of American blood donors.

Interferon itself was only recognized because of advances in modern biology and the ability to study hepatitis and the virus that causes it has required some of the most sophisticated new research methods.

Most M.D.'s practicing today would be bewildered by even the summary of the report I referred to because it is so much a product of recent research. But the report says that a new treatment for hepatitis—administration of interferon—has been found.

To extend this critical work further will require a source of human interferon and new ways to analyze hepatitis virus. Both needs could be met by recombinant DNA work, but the needed experiments would be difficult to perform under the present guidelines.

They will, I hope, be done anyway, but it should be realized that the pace of future biomedical research may depend critically on the nature of the recombinant DNA guidelines. Those guidelines should only be as stringent as required and maintaining the flexibility to downgrade them is in the national interest.

My second comment relates to the likelihood that the guidelines are too stringent.

In the laboratory we insert DNA into bacteria by treating them with calcium. I have recently realized that the conditions used in the test tube are probably reproduced daily in the intestines of millions of people.

Every time a teenager drinks a quart of milk, he produces the optimum condition in his intestine for having his bacteria take up DNA. Conditions that at least somewhat facilitate DNA uptake probably occur in all of us much of the time.

In our intestines we continually shed DNA from our own cells. Bacteria taking up human DNA is therefore probably a commonplace of life. A fast calculation shows that the human population sheds at least a million pounds of DNA a day into its intestines and produces more than a billion billion bacteria a day. All of this in conditions often facilitating the uptake of DNA by the bacteria.

If this argument is right—and we are now trying to obtain evidence about it—then the major worry leading leading people to want to increase the stringency of the guidelines is nonexistent, and it will be very likely that we shall want to reduce their stringency in order to facilitate the important work of modern biology.

I therefore trust that whatever procedures you follow to extend the guidelines incorporates into them a method for maintaining flexibility.

I would personally recommend that the NIH, or one of the committees of the NIH, maintain the responsibility of changing the guidelines because if it is necessary to change the guidelines to go through the whole process we have been going through recently with interagency committees and whatever else, I have the fear that nobody ever will ever want to undertake a change in the guidelines, where I think that may turn out to be very much in all of our interests.

Senator KENNEDY. I obviously would agree. I think that those that review the guidelines—at least I do—is a prudent step, but it certainly should not be fixed.

If it is not necessary, it should be lifted. And yet if we find out if there are more stringent requirements, those should be considered as well.

Dr. BALTIMORE. Absolutely.

Senator KENNEDY. Dr. Sinsheimer.

Dr. SINSHEIMER. Mr. Chairman, I would like to say, first, that while, for reasons I will indicate, I believe the guidelines for recombinant

DNA research are presently inadequate, they are certainly far better than no guidelines. They are intended to protect the public.

I therefore support their extension to cover all research activity in this field, however supported and wherever performed.

With respect to the specific question of the extension of the guidelines to industrial research activity, I would point out that this research does not require elaborate facilities and large capital investments. There is no reason to believe it will be limited to large pharmaceutical companies with proven records of care and reliability.

Further, the virtual certainty of the development of new techniques and of the extension of these techniques to additional organisms and higher life forms will require a free flow of information, the continuing updating of guidelines, and the continuing scrutiny of this field of research by a body which will endeavor to reflect the public interest.

As I have said, I believe the guidelines, valuable as they are, are presently inadequate. I believe they do not provide sufficient recognition of the fact that we are here creating novel living organisms—unprecedented in the evolutionary order.

As living organisms, they are self-perpetuating and destined to their own individual evolution. I do not believe we can predict the properties of these organisms—created by the fusion of genes from disparate species—or their subsequent evolution, or their impact, present and future, on the existent biosphere. We do not know that there is a hazard here, but neither do we know there is not. If such hazards exist or develop, it will be, in this instance, uniquely irreversible.

In these circumstances, I feel much more caution is appropriate than I find in the present guidelines.

To make a slight addendum in response to Dr. Baltimore's addendum, I feel that my associates in this field characteristically tend to underestimate the significance of what has been accomplished.

Senator KENNEDY. If it was the worst that you could imagine, what would you describe?

Dr. SINSHEIMER. Well, the worst, of course, would be a sort of biological chaos.

Senator KENNEDY. What does that mean in layman's language?

Dr. SINSHEIMER. The creation of new forms of pathogens, or new forms of pests, organisms that would disrupt the equilibria that, more or less, exist at any given time in the course of evolution between different life forms.

Senator KENNEDY. That would have dramatic impact in our environment and our life environment?

Dr. SINSHEIMER. I would think it could. On the whole life support system.

Senator KENNEDY. What do you think, on the other hand, are the benefits?

Dr. SINSHEIMER. The benefits are some of the things that have already been mentioned, the possibilities of significant new knowledge of value in medicine and agriculture, the possibilities of producing certain compounds of importance to man, such as interferon that was mentioned, hormones, antibodies, things of that kind. Possibilities of developing new crop forms that would be superior to those we have available to us.

Senator SCHWEIKER. Doctor, some scientists say that we can get a lot of this through normal genetic engineering, with a lot less risk. Do you concur with that point of view?

Dr. SINSHEIMER. I partly concur. I think some of the things that are being done with recombinant DNA techniques could be done by other techniques.

I think also it is possible that by considerable amount of ingenuity some of the other projected benefits might be achieved by less dramatic means. I do not know that that is entirely true.

Certainly, at the present time, there are no alternatives for certain kinds of experiments.

Senator SCHWEIKER. Do you see the opportunity for the advancement of mankind as outweighing the risks?

Dr. SINSHEIMER. I think so, if it can be done under sufficiently confined conditions.

Senator SCHWEIKER. You are quoted in the New York Times as saying:

"What we are doing is almost certainly irreversible. Knowing human frailty, these structures will escape, and there is no way to recapture them."

Is that accurate?

Dr. SINSHEIMER. In my judgment that is an accurate statement.

Senator SCHWEIKER. Is that not pretty high risk?

You said a moment ago, and I am not disagreeing with you, that the benefits outweigh the risks. But if this is a situation where we can expect the inevitable escape of these structures and there is no way to recapture them, and in light of what you said a few moments ago to Senator Kennedy, the risks are indeed high here if human frailty goes its normal way; are they not?

I am a layman, I do not know.

Dr. SINSHEIMER. Well, you would have to somehow balance what I would regard as the certainty that these organisms will escape the laboratory against the potential benefits, and the uncertainty of the hazard. It becomes some kind of balance that you have to come to.

Different people will see that differently, I am sure. Different groups in society will see that differently.

One of the complaints that has been raised against the guidelines is that they were devised by scientists, and really directed toward the immediate health hazards that these scientists could foresee. And that they did not perhaps adequately take into account the concerns of other sectors, that other sectors of society might have, or the fact that this knowledge, while it was devised by scientists for the solution of their own scientific problems, is at the same time available to all sectors of society.

It is available, obviously, to industry, to the military, to potential subversive groups, to amateurs, if they want to use it, and one has to consider those factors, too.

Senator SCHWEIKER. It is available to amateurs? Is it not also true that it is fairly inexpensively available?

Dr. SINSHEIMER. Moderately. One of the aspects of this field, it seems to me, is, it is much less expensive than the nuclear field to which it has been compared. An investment in a laboratory to do this work is perhaps $50,000 to $100,000. That is not trivial, but it is not billions.

Senator KENNEDY. If the Senator would yield, would you agree that in terms of magnitude, it is as great in significance as the splitting of the atom?

Dr. SINSHEIMER. I think what this technology does is to make available to us the accumulated gene pool of evolution in all organisms.

We can now take genes from any organism and recombine them in any manner we wish. I do not think my colleagues would object to that statement.

To my mind that is an accomplishment of significance equal to splitting the atom, or transmutation of the elements. It is literally unprecedented in 3 billion years of evolution.

Senator SCHWEIKER. I do not want to oversimplify what you are saying. I am trying to comprehend, as a layman.

You are saying, in essence, that all that has gone before, we now have the power to change to some degree. We have the power to accelerate, decelerate or in some way alter the evolutionary process?

Dr. SINSHEIMER. Yes. I would agree with that.

Senator KENNEDY. I suppose we are talking about eventually really making decisions whether we have big people, tall people, short people, blue eyes, green eyes, blond hair?

Dr. SINSHEIMER. If you extrapolate this to human beings, which is a pretty long extrapolation, yes.

Dr. ZINDER. Might I interject something here?

Senator KENNEDY. Yes.

Dr. ZINDER. I certainly agree with my colleague about the profundity of what has been done.

Senator SCHWEIKER. Use the microphone, please.

Dr. ZINDER. I agree with my colleague about the profundity of what is being done with regard to our ability to take genes from any organism and move them around.

However, I have the feeling that he tends to look at the profound nature of the event in a pejorative way. I prefer to not consider it dangerous, or not dangerous, but rather as a profound thought with which we should be concerned. But it does not predict, at least to my mind, hazard. Man has been doing this since recorded history.

This is no more a profound event than the development of agriculture was to the history of man, and what happened. The cultural innovation is just as irreversible as genetic innovation.

One of my colleagues, a geneticist, has done an analysis of cultural evolution, analysis of the spread of mutations.

Ideas occur, and they spread. They are irreversible.

I think Dr. Sinsheimer has raised a very serious issue. I do not think it should be put in terms of its danger. I think it should be thought of as something important, more a philosophical point relating to the future of mankind, and it is in that vein that we should discuss this.

Senator SCHWEIKER. If man has been doing this before, the evolution of change has involved a time factor. As I understand what some of you folks are saying, we are compressing the time factor, if not, for all intents and purposes, eliminating it. In the past, such changes took hundreds of thousands of years to evolve. We now have, with new technology and proper techniques, a way of eliminating the time factor in this evolutionary change process.

Is that not a new element from before?

Dr. Zinder. It certainly is a new element. I say the words "new element". I do not believe that by saying something is new or novel it is necessarily a dangerous element. That would mean that a great deal of what we do in an innovative and creative sense is dangerous, and I think the emphasis should not be put on that point.

The emphasis is on the new, and it is profound, and it is going to, I believe, create a revolution, the second revolution in molecular biology.

I just disagree with him on the way you present this argument.

Senator Schweiker. Before, with the evolutionary process—which would be a snail's pace compared to what we can do now—if we made mistakes, we would have time to correct them, and the implications of mistakes, it seems to me, would be spread out over a much broader time frame than they would be now.

Is it not true that if we make one mistake here—well, we do not have 200,000 years to digest it before something goes wrong with mankind as a result?

Dr. Zinder. This gets into really terribly complex biology, and evolutionary theory——

Senator Kennedy. Well, before we do that—well, go ahead and finish your response to Senator Schweiker, and then we will get Dr. Holman into this, and then come back on this.

Senator Schweiker. You have a chance to respond in some way if you want to.

Dr. Zinder. I've finished.

Dr. Sinsheimer. Could I add one thing, Senator?

I would like to say it seems to me we are doing more than just accelerating evolution. Evolution has always proceeded in a kind of linear manner which each organism evolving into the next step without a broad exchange of genes between different species—in fact, just the opposite.

Recombination of genes has been restricted to within species. What is happening now, it is possible, as I said, to take genes from all the species that have evolved, and put these together in novel combinations, and that is something totally new in evolution.

Senator Schweiker. Laterally, as well as lengthwise in terms of dimension concept?

Dr. Sinsheimer. Yes.

Senator Kennedy. Dr. Holman?

Dr. Holman. My name is Halsted Holman. I am professor of medicine at Stanford Medical School.

Senator Kennedy and Senator Schweiker, the main arguments of my written testimony dealt with three points, they were: (1) the need to extend the guidelines to all activity in the recombinant field; (2) the need to reduce haste in the pursuit of recombinant research while we learn more about its consequences; and (3) the essential need to improve dissemination of information to the public and to assure a public role in decisionmaking about science policy including recombinant DNA.

I do not wish to read that testimony.

There were two additional points which I wish to dicuss at some time. I am not sure they are pertinent now.

Senator Schweiker. Go ahead and list them now.

Dr. HOLMAN. The first one has to do with the question that came up earlier about the use of enfeebled *E. coli* as the vector agent in the research. It is a concern that I think is valid, although I am not entirely sure of all the discussions that went into the guidelines. With that proviso I would like to explain what I mean.

Central strategy in recombinant DNA research involves the use of weakened bacteria, such as *E. coli*, which presumably will not survive outside of an artificial laboratory environment.

As far as I can judge from the evidence there is a real possibility that is true.

The point I want to raise, and which appears to me to be a weakness in the guidelines, relates to the problem of human susceptibility to *E. coli* infections.

I am not now talking about enteritis. I am talking specifically about bloodstream infections in which the outcome is roughly 30 to 50 percent fatality.

The point of the comment is, in the past 20 years, from 1951 to 1971, there has been a tenfold increase in the incidence of bloodstream infections in major hospital centers from gram negative organisms, which is the family to which *E. coli* belongs.

Of these infections, roughly 37 percent have been due to *E. coli*. And the slope of incidence of these bloodstream infections continues upward.

Now, the reason for this increasing incidence is not clear. But there are some probable answers.

First, we have an increasingly elderly population, requiring increasing amounts of health care. As people age they apparently become more susceptible to organisms like *E. coli*.

Second, we have an increased prevalence of chronic disease, which reduces resistance to infection.

Third, we use many more invasive procedures; that is, put tubes into people in the process of diagnosis and treatment. These procedures have become one of the major sources of disseminated infection, such as *E. coli* infection.

Fourth, we use a wide variety of drugs which inhibit the immune response.

These reasons are not temporary. They reflect circumstances that are permanent, namely, the aging population, the complexity of medicine, the use of more powerful drugs and procedures.

Thus I think one can say that counterposed to the question of enfeebling the bacteria is the problem of the susceptibility of enfeebled hosts.

What this means in terms of dissemination of an enfeebled bacteria, I do not know. I would like to raise two or three points with regard to this specific issue.

As far as I can judge from the guidelines, this question was not addressed. Its relevance relates to the monitoring of the effectiveness of biological containment. For example, individuals who work in the recombinant program may become infected with small amounts of enfeebled bacteria, not become sick themselves, and potentially be carriers who could infect others. Such carriers might be very difficult to detect.

Much research on recombinants is done in a medical center where there is considerable exchange between the people working in the laboratories and people seeing patients. Sometimes the same person does both. Thus we have a different epidemiological problem from the one envisioned in the guidelines. It is the problem of enfeebled bacteria interacting with persons whose resistance is compromised.

It is a question of the epidemiology of infection of weakened hosts with altered bacteria. The techniques for monitoring and control are, at least to my knowledge, not well developed. The problem underscores the necessity for prudence in conducting recombinant research.

Senator KENNEDY. If we could get back to one of the questions that we raised earlier, and that is the role of the public and the local communities in terms of these issues. Let us discuss the extent that they ought to be notified, the general kind of discussion and involvement of the public in terms of these things.

As a sort of opening comment, what is the best way to proceed? How should we be proceeding?

Dr. HOLMAN. Are you speaking to me?

Senator KENNEDY. Yes.

Dr. HOLMAN. That was my second point.

Briefly, I outlined in the written testimony what I thought were very positive events that have happened. They include testimony before this committee, and NIH hearings, and the meeting at Airlie House, and meetings and activity of the National Committee on the Protection of Human Subjects. Now I would like to stress a countervailing negative trend that is equally important. It can be summarized in the following ways.

First, the problem of conflict of interest in setting the guidelines. By and large the work was done by very well meaning, highly intelligent and motivated people, who nonetheless work in the field. There was participation of only very modest numbers of persons outside of molecular biology. Furthermore the same agency, the NIH, that supports the research is establishing the regulations.

The second negative development is the proposal of patents, which seems to me to be a direct step toward removing the issue of recombinant research and its safeguards from public domain, placing them in the private domain.

Now, I understand that there can be conditions made on patents, but my amateur's understanding of patents does not change the fact that the control passes from public to private mechanisms.

There is also the issue of review of the effectiveness of the guidelines, which is barely discussed in the guidelines. Review relates to the question about enfeebled strains and epidemiology, but beyond that there is no specification of either processes or public role in the review.

Finally, there is the issue of the expiration of the mandate for the National Commission on Protection of Human Subjects, which presumably would have a lot to say about these matters.

You can ask what should be done. First, I think the mandate of the Commission should be extended, and the Commission should be given authority over this field of research.

Second, the NIH should be asked to expand its guidelines in the area of epidemiology, and publish specific review mechanisms. It should insure public participation at every level of review and revision of the guidelines. Third, the Government should deny patents with regard to recombinant technology.

Senator KENNEDY. Maybe some of the others would like to comment.

Dr. BALTIMORE. I certainly agree on the patent issue, that a patent should not be a way of restricting the control of recombitant DNA research.

Again, with very little knowledge about patent law, my understanding is that the patenting process itself is not restrictive as long as patents are held in the public—held by the public, possibly through NIH. I think it may provide some order to the development of this field if patents are in fact issued, but I would hate to see those patents under the sole control of any small group of individuals, or any specific universities, even.

Senator KENNEDY. Let me just raise this point. In the areas of the universities, how many do we have now that are doing the research? What would you estimate is the number of universities where this kind of research is taking place?

Dr. BALTIMORE. Fifty.

Dr. SINSHEIMER. Thirty.

Senator KENNEDY. Well, 30 to 50.

As I understand it, there have only been two communities, Michigan and Cambridge, Mass., where the communities have raised these issues, and where there has been interagency and discussion.

How do you receive involvement of both local communties? Should they be made aware of the kind of activities taking place?

Should they be informed? How are we going to develop a process by which you can have an informed and balanced discussion which is intelligent, and which will help people understand this problem? Or should we just say, in the promulgation of the reguations, on sort of the bottom paragraph, in very small script, just say, well, if they ask, you should respond, and their views should be considered, and what their views are will be made as part of an application?

How are we going to do that in a way that makes some sense?

Dr. ZINDER. I would just like to respond to that in the following way.

There is an aspect to this subject that makes it intrinsically very difficult to discuss. That is that in every instance we must talk about potential, whether it is potential benefit, or potential hazards.

We have no way to quantify in either direction. Therefore, while I agree, and we must bring this to the attention of the community——

Senator KENNEDY. Can they not understand that?

Dr. ZINDER. It becomes very difficult, because there are people who say the experiments are very dangerous, and it is very easy to say there are great dangers, and they can always ask how can you assure us there are no dangers. That is impossible to answer.

But on the other hand, there is no instance that we have for the worst scenario that we know how to write, and we can write pretty bad scenarios with this technology, that it really would obtain.

There is no evidence that it really would obtain. In fact, it would be worthwhile for someone to do a few experiments in a safe house to find out whether or not such creatures would survive in nature.

Very often when you put a piece of DNA inside another piece of DNA they do not like to stay together for a variety of reasons, which are scientifically complicated to explain.

This is a fact we have to deal with.

Senator KENNEDY. What is your conclusion on it? Complex? Difficult? Difficult for people to understand the potential danger, can be emotionalized? What is the bottom line?

Dr. ZINDER. We try very hard to talk to everybody that calls us, explain it to them, open our files, in a sense, to try to be as honest as we can, but try to explain to them that we really cannot give them solid information. It just does not exist.

There is a certain nuance in the discussion that in vitro recombinant DNA is a dirty word, and I do not think that is the case.

Could I take the opportunity to make one little announcement?

Senator KENNEDY. Yes.

Dr. ZINDER. I just want, as a member of the National Academy of Science, to announce that the Academy has passed a resolution which strongly endorses the adherence to these guidelines.

Senator KENNEDY. Dr. Sinsheimer?

Dr. SINSHEIMER. In response to your concerns about the public involvement, which I think are very impotrant, I would like to say two things.

First, I would like to endorse Dr. Holman's suggestion that a national commission explore this question, particularly with respect to developing the attitudes that various sectors of society will take toward the issue after it has been explained to them, and after they have had time to reflect on it.

Second, with regard to involvement at the local level, I would point out that the guidelines recommend that the institutional biohazards committees have representatives of the local community on each such committee.

I think that is extremely important. And through those people it may be possible to develop a dialog with those in the communities who are concerned.

Senator KENNEDY. I am going to have to leave in about 10 or 12 minutes. I know Senator Schweiker has a few other areas of questioning.

I think we ought to really insist that in those communities that want this discussion, who want this knowledge, who want to have a comment and input on it, there ought to be some mechanism by which they can do so.

We are very interested in trying to work with you in seeing how this should be done. Obviously, maybe just in terms of the record, you can give a response—I just heard the buzzer for me to go over on the floor.

How can this best be done? We want to work with you and other members of the community in seeing that it is done.

Maybe you can make whatever comments, and evaluate it in terms of the record.

Senator SCHWEIKER. Would you like to respond?

Dr. BALTIMORE. I would like to point out that the actions in Cambridge and Michigan are really not the community rising up with interest on recombinant DNA, but rather an aspect of the self-policing process within the scientific community. Because in the Cambridge situation, which I know very closely, it was people on the faculty of Harvard and MIT who first raised the issue and brought the issue to the city council.

Effectively the city council was a mechanism, a public mechanism for concerns that came out of the scientific community.

Similarly, the situation in Michigan arose from members of the Michigan faculty who felt that the process that was being gone through then on the Michigan faculty was inappropriate.

So, that to a large extent I do not think we have seen true local community interest in the problem very widespread, in spite of the enormous publicity that it has had. Therefore, I am not sure that the problem that Senator Kennedy raised of mechanisms for interchange is, in fact, a real problem.

Dr. HOLMAN. I understand the issue that has been raised, and I think there is some contrary evidence on this precise point.

I would like to call your attention to a study, the reference to which I cannot remember but it was published in Science about a year ago. It was a very interesting examination of public attitudes toward science and technology in California. The essential conclusions were that there was a great deal of public interest in these matters, that the respondents were overwhelmingly not simple-minded in their evaluation of the benefits and problems of science and technology, that they had an enormous respect for science and its benefits, and that they had insisted that the development of science occur through channels of public authority in which they, the citizens, would have a major role.

It is a worthwhile study on precisely this point. It tends to confirm the experience of physicians indicating the extraordinary ability of people to understand complex problems when an appropriate way of presenting the information is developed.

Senator SCHWEIKER. Dr. Sinsheimer, do you want to comment on Senator Kennedy's earlier question at this point?

Dr. SINSHEIMER. You mean the question with respect to public involvement?

Senator SCHWEIKER. Yes, but first, let me pursue another point along this line. One of the panelists, I forget who it was, ranked this development as equivalent to nuclear energy, or perhaps beyond nuclear energy.

Who made that statement?

Dr. SINSHEIMER. I did.

Senator SCHWEIKER. I gather that, impactwise, you feel that the impact of this research development is greater than the impact of the development of atomic energy.

Dr. Sinsheimer, you apparently have already expressed the opinion that it is greater, is that correct?

Dr. SINSHEIMER. It is comparable.

Senator SCHWEIKER. Would the other panelists agree with that?

Dr. BALTIMORE. I would, in fact, say it is quite different than, and probably much more important than the development of atomic energy.

I would not want to focus just on recombinant DNA research, but rather on the whole thrust of modern molecular biology.

Modern molecular biology is leading us to the point where we have ability to manipulate genes, and manipulate the essence of life, if you wish, of various organisms under various conditions. And the change in that will bring to our perceptions of ourselves and our ability to control ourselves, I think, will outweigh atomic energy, which brings.

on the one hand, at the moment a certain fear of atomic explosions, and on the other hand, fears of the consequences of alternate forms of energy.

I expect modern biology will provide that change, and therefore, in fact, requires the kind of continuous scrutiny that your committee has been giving it.

Senator Schweiker. Nuclear energy was primarily developed in wartime, under secret conditions. It was considered a top military secret.

Here we are bringing new development in, not in wartime, not in military secrecy, and I think we have to deal with a whole new series of questions as to what responsibility we have to the public in terms of presenting the options to them, the risks to them, and the benefits to them.

It seems to me, as much as I commend the faculty for bringing this particular situation to the attention of the Cambridge City Council, that we as Federal legislators have far greater responsibility here, in view of the comparability of atomic energy.

While there have obviously been some lay articles, such as I quoted from this morning, most of the information relating to this research has been in scientific journals. I think one of the reasons Senator Kennedy is chairing this hearing, and I concur, is that there is certainly some kind of responsibility on the Congress part, and this committee's part, to point out the risks and benefits in this situation, which you admit is comparable to the development of atomic energy and in many ways may have a greater impact than atomic energy on our lives.

I just wonder what else we can do as a Federal legislative body to alert the public not in any sense of shocking, or frightening, or scaring the public, of course, but I think we do have a responsibility to get the implications of these developments through to the public. I do not really feel that the potential impact of this research has come through in the scientific media to the public, as much as scientists may have tried to express the implications of where we are going.

Maybe some of you want to comment on that, or disagree with that, or add to it.

What responsibility does the Government have in this area? Beyond guidelines—and I think the responsibility goes far beyond guidelines—what responsibility does the Government have in terms of the basic issue itself?

How do you, as scientists, see our responsibility?

Dr. Holman. In a sense, this is a reiteration. I think the single most important recent development in science policy was the establishment of the Commission for the Protection of Human Subjects. The work of that Commission has clarified issues and allowed accurate, useful policy development in highly emotional and controversial fields, such as fetal research.

It has established a mechanism whereby information can be disseminated to the public and, through hearings and other such approaches, whereby the results of the public considerations can be brought back to the policymakers.

It is my understanding that the mandate of the National Commission expires in the next few days. If it is not renewed in this session of Congress, it may be very difficult to reestablish the Commission.

To my mind, therefore, the most important step right now would be for Congress to review that mandate, and expand the authority of the National Commission to cover all aspects of science policy. Then, through that vehicle, one could develop local and regional meetings, which could be tied in with the review of the NIH guidelines on recombinant research, but also going substantially beyond into science policy generally.

I am not playing a debating trick, but the initiative right now is in Congress hands with the impending expiration of that mandate of the single most useful Federal body for developing public participation in science policy determination.

Senator SCHWEIKER. I would very strongly agree with that statement.

I do want the record to show that the Senate has in fact passed that bill, and met its responsibilities.

Dr. HOLMAN. The House has not.

Senator SCHWEIKER. Are there any other comments?

Dr. Zinder, do you have any comments that you would like to make on this subject?

Dr. ZINDER. It seems to me that the Congress should continue to keep itself informed of what is going on in this area, as it is doing now by hearings such as this. See that the National Institutes of Health and its Directors are moving forward, fund the appropriate and necessary containment facilities.

That is an important aspect which people have not mentioned in the guidelines, that they are going to cost money, like most things. If we want the research to go forward, and I think most of us do in one way or another, it is going to cost money in order to build special facilities to protect the public.

As you know, the main source of funding in this area would be the Congress.

I would like to make one comment about the awareness of the public in this area that you mention.

It is true the public does not read the scientific literature. But I can think of few issues relating to science that has been so much in the popular press as the issue of recombinant DNA. From the time of Asimolar Conference, it certainly has been covered very deeply by the Washington Post and the New York Times and other newspapers. It has been before the public.

Senator SCHWEIKER. I think to some extent that the development of our technology in general and the growth of scientific achievement has been so phenomenal that people tend to put it all into one category, into one bowl of soup.

Here you are telling us this morning it is not only not in one category, not in one bowl of soup, it is comparable to splitting the atom and probably more far reaching than that to some extent.

I do not think anybody who reads these articles of a lay nature has that perception. That is my great concern. You scientists do grasp that concept. You assess it. You perceive it. It is part of your being.

I just do not get the feeling among the lay community, as much as the articles have been in the popular press, that the full significance of this research has been perceived.

It is simply another new thing, like a new transistor. That is really in my judgment how the public has regarded this development.

I feel some responsibility to do what Cambridge and Michigan have done; to bring the issue to focus, the kind of focus that seems to me to be needed to drive home the things that have been reported in the press.

But I think so far the press reports to the public have been regarded in terms of traditional technological achievement, as just another example of the great ingenuity of American science, a breakthrough of the sort that is continually occurring, without any differentiation between technologies and achievements in the popular mind.

Does anyone else have a comment?

Dr. SINSHEIMER. One matter that the Congress might take up, although I think it is probably a little premature as yet prior to consideration by a Commission, such as Dr. Holman mentioned. Sometime it may be desirable to establish some kind of regulatory body comparable to that which has been set up in the nuclear field, where, as you know, the research arm has been separated from the regulation arm.

Similarly, in this area, that may become necessary. NIH, which sponsors the research, very likely is not ultimately the proper body to regulate the same research. That may be something Congress should explore at some time.

Senator SCHWEIKER. I want to thank the members of the panel very much for your participation and appearance here this morning.

I think your expert testimony is most helpful.

Thank you for taking the time to be with us.

[The prepared statements of Dr. Baltimore, Dr. Zinder, Dr. Holman, and Mr. Sinsheimer, follow:]

by David Baltimore, PhD.
American Cancer Society
Professor of Microbiology
Massachusetts Institute of Technology

TESTIMONY FOR SENATE HEALTH SUB-COMMITTEE HEARING, September 22nd, 1976

Contemporary research in basic biology has been more productive of knowledge about living systems than of information useful in the treatment of disease. The lack of practical advances stems from the complexity of the problems; the available techniques can be used on bacteria but not readily on higher organisms.

"Recombinant DNA technology" has the potential to make modern biology more relevant to the problems of human disease. This new way of studying genes simplifies complex biological problems so their individual parts can be analyzed. A deeper understanding of how the systems in human beings function is sure to come from these new methods. From this new understanding, novel methods are likely to evolve for preventing and treating the presently unconquered diseases that afflict us. Recombinant DNA research is our best hope for understanding diseases like cancer, heart disease, and malfunctions of the immune system, for which the prospects are poor for prevention solely by public health measures.

When the possibility of recombinant DNA research first appeared on the scientific horizon, the community of molecular biologists became concerned that there might be hazards in the work. This concern was rapidly transmitted to the public. Over the last three years many biologists have participated in the unprecedented examination of how recombinant DNA work should be regulated, a process that involved them in assessing the magnitude of the risk. To most biologists the risk appears small and controllable but nonetheless they have concluded that stringent regulation is worthwhile until precise knowledge is available. Hopefully, such knowledge could allow the lowering of barriers to unfettered research.

The NIH guidelines provide stringent procedures for the conduct of recombinant DNA research. While I would hope that in the future the guidelines might be proved overly restrictive, at present they seem to be an appropriate framework for allowing recombinant DNA research to go forward.

As presently formulated, the guidelines apply only to research funded by NIH. For work to proceed with maximum safety, the guidelines should apply to all recombinant DNA research, whatever its source of funds. It is especially important that non-academic laboratories be covered.

It is also important, however, that the process of extending the purview of the guidelines not jeapordize the ability to modify them. The guidelines were formulated according to the recommendation of the Asilomar meeting that safeguards be set high and reduced if experience warrants reduction. As research in the area continues, we can expect to want to change details, extend coverage to newly recognized experimental situations, and possibly reduce assessments of risk.

by David Baltimore

ADDENDUM TO TESTIMONY FOR SENATE HEALTH SUB-COMMITTEE HEARING, September 22, 1976

Although they are not in my written testimony, I should like to add two comments about the question of safety.

The relevance of advances in modern biology to problems of human health has been questioned repeatedly. I think this is a problem of seeing the future in terms of the past--the September 2, 1976 issue of the New England Journal of Medicine is I think a better guide to the future. One article there describes the use of a substance called interferon to treat the very serious disease of human hepatitis. A million people in the world are chronic sufferers from this disease including more than 1 per thousand of American blood donors. Interferon itself was only recognized because of advances in modern biology and the ability to study hepatitis and the virus that causes it has required some of the most sophisticated new research methods. Most M.D.'s practicing today would be bewildered by even the summary of the report I referred to because it is so much a product of recent research. But the report says that a new treatment for hepatitis, administration of interferon, has been found. To extend this critical work further will require a source of human interferon and new ways to analyze hepatitis virus. Both needs could be met by RD work but the needed experiments would be difficult to perform under the present guidelines. They will, I hope, be done anyway but it should be realized that the pace of future biomedical research may depend critically on the nature of the RD guidelines. Those guidelines should only be as stringent as required and maintaining the flexibility to downgrade them is in the national interest.

My second comment relates to the likelihood that the guidelines are too stringent. In the laboratory we insert DNA into bacteria by treating them with calcium. I have recently realized that the conditions used in the test tube are probably reproduced daily in the intestines of millions of poeple. Everytime a teenager drinks a quart of milk he produces the optimum condition in his intestine for having his bacteria take up DNA. Conditions that at least somewhat facilitate DNA uptake probably occur in all of us much of the time. In our intestines we continually shed DNA from our own cells. Bacteria taking up human DNA is therefore probably a commonplace of life. A fast calculation shows that the human population sheds at least a million pounds of DNA a day into its intestines and produces more than a billion billion bacteria a day. All of this in conditions often facilitating the uptake of DNA by the bacteria! If this argument is right, and we are now trying to obtain evidence about it, then the major worry leading people to want to increase the stringency of the guidelines is nonexistent and it will be very likely that we shall want to reduce their stringency in order to facilitate the important work of modern biology.

STATEMENT
OF
NORTON D. ZINDER, PH.D.

PROFESSOR
THE ROCKEFELLER UNIVERSITY
NEW YORK CITY

BEFORE THE
SUBCOMMITTEE ON HEALTH
LABOR AND PUBLIC WELFARE COMMITTEE
UNITED STATES SENATE

SEPTEMBER 22, 1976

Mr. Chairman and members of the Senate Subcommittee on Health:

I am honored to participate in your examination today of an important subject. With your indulgence, I would like to begin by reviewing my professional background because it is relevant to the issues we face.

I am a professor of molecular genetics at The Rockefelle University. In the early fifties, with Joshua Lederberg, I discovered bacterial transduction--the ability of certain bacterial viruses to pick up genes from their bacterial hosts and transfer them to their next host. A few years later Edward Adelberg and Francois Jacob discovered that the plasmid, called F, could also pick up genes from its host and transfer them to another host. Thus, in a sense, the new laboratory techniques for constructing combinations between (a) bacteriophage or bacterial plasmid genes and (b) genes from other organisms, have brought the events in my career full cycle.

Let me explain this. What I discovered that nature does in some special instances, scientists now can do at will. The natural processes are probably a form of primitive sexuality: the interchange of genetic information between organisms. The laboratory-contrived equivalent is also a form of sexuality, except that the range of species involved --as well as the source of the genes that can be transduced-- may be infinitely broader. I should add that, when considering the issue of recombinant DNA, some reputable scientists feel that transduction-like processes occur continuously in nature. However, scientists generally believe that this does not occur between species that are distantly related to each other.

To continue with an account of my own background, I am presently a member of the Executive Committee of the Assembly of Life Sciences (Alsec) of the National Academy of Sciences. This committee sponsored the meeting at the Massachusetts Institute of Technology on April 17, 1974 that led to the now famous Berg _et_ _al_ letter published in _Science_ and _Nature_ in July 1974. Parenthetically I should mention that I helped to organize the meeting, attended it, assisted in the drafting of the letter, and of course, signed it. I am pleased to be able to inform you that a resolution has been approved by Alsec of the National Academy of Sciences "strongly endorsing adherence to the NIH guidelines by all research and educational institutions, private industries and individuals involved in work with recombinant DNA, regardless of the source of their support."

In addition, the Academy, through Alsec, is setting up a standing Committee on Laboratory Created Biohazards, which will be concerned not only with the recombinant DNA issue but also with research in other areas of science, attempting to anticipate the appearance of comparable issues. However, as its first order of business, this N.A.S. standing committee will encourage the establishment of a regular program of assessments of the recombinant DNA guidelines and participate with other interested groups in such assessments. We expect that this committee will also provide unbiased input to the N.I.H. in its continuing reevaluation of the guidelines. We feel that the technical competence, the moral authority, and the traditional prestige of the Academy can be helpful in promoting voluntary adherence to the guidelines. The Academy can also provide another forum for the necessary, serious dialogue between various groups concerned with the issue of in vitro recombinant DNA.

Now I want to discuss the nature of the guidelines. The history of their development is well-documented beginning with the original Singer and Soll letter, then the Berg _et al_ letter, through the Asilomar conference and its provisional guidelines, culminating in the current NIH guidelines. Not surprisingly, at each stage there were arguments for the extreme positions. Some individuals said that the guidelines were too lax, and some said they were too stringent. Despite broad discussions both in the scientific community and in the media, some individuals even claim that the guidelines were prepared in a closed, irrational, unscientific and undemocratic manner.

I believe that the guidelines are reasonable. They may be too stringent, but I join my colleagues in choosing to err on the side of caution. Although I could nitpick over details, I recognize that any set of regulations--especially for research which, by definition, has many uncertainties--could never be perfectly satisfactory to everyone.

I should point out that a totally independent group of scientists in Great Britain has come up with a notably similar set of guidelines for these experiments. This indicates that while the individuals who were involved recognized the many unknowns in this area, there was a widely shared intuition about the issues that led competent and independent groups to a similar set of conclusions regarding the conceivable hazards of any particular experiment.

Let us confront these conceivable hazards. To begin with, there is no convincing evidence for any of the more horrendous scenarios about the consequences of the use of this new technology. Indeed, the opposite is true: there are sound epidemiological and biological reasons for arguing that--even though living organisms are involved and therefore could multiply--there would be little potential for their spread if they escaped from the laboratory. Laboratory-adapted creatures tend to run downhill; they become less virulent.

What about the potential benefits of this technology? We would not be talking about guidelines unless this field reflected a very important scientific advance with, in the words of Joshua Lederberg, "uncertain perils and certain promise." Recombinant DNA technology is a very powerful tool for the investigation of a host of scientific problems that are unapproachable by other means. At the moment the potential benefits to man will emerge from the detailed analyses of the structure of chromosomes and the mechanisms of control of gene function in many organisms. This will lead to a deeper understanding of normal and abnormal physiological processes and, perhaps, to the creation of agriculturally important microorganisms. The other benefits, such as inexpensive synthesis in microbes of human proteins that are in short supply--insulin, for example--must await further research.

Personally, I prefer not to promise specific results. It has always seemed to me that some scientists overpromise, thinking that this is the only way to obtain support for research. The argument should be reversed. We should not promise specific dates or results as we try to meet our mutual goals of benefiting man by doing certain researches; one reason is that even when a process is understood at the deepest molecular level, there may not be much we can do about it immediately, for example, with sickle cell anemia. What we can say is that if we don't do the research, the benefits will never be obtained; that is certain!

I have one more series of comments to make about the issue of recombinant DNA. I believe these comments are pertinent for your Committee. But my comments are even more broadly concerned with the tone of the public discussion and with the motives of the scientific community.

I have been associated with this field from its birth. Scientists discussed these problems long before the recent publicity. I know almost all of the individuals who have been involved in the research and in the efforts to regulate some of the research. Our original efforts to frame guidelines were applauded to a degree that surprised us; we felt that we were simply being socially responsible. As time has passed since the Berg _et al_ letter was published, a much more negative tone and attitude have appeared. Some observers have gone as far as questioning the motives of the scientists working in this area.

However, I believe that scientists usually have been socially responsible. They are generally credited with putting atomic energy into civilian rather than military control. They tried to bring to the fore the idea that the world would be a better place were a hydrogen bomb not developed. They have been in the forefront of international discussions on arms control and led the way to drafting the covenant on biological warfare and the treaty on the nuclear weapons test ban. More recently, they have been very active in the environmental movement. This is not to say that we are descended from the angels, for there certainly are uncaring or irresponsible scientists.

On the specific issue of recombinant DNA, some of us are now in the awkward position of having our colleagues ask us, "what have you done to the future of genetic research?" They appreciate the potential problems with this technology, but feel they could have handled it in their own labs, just as many other difficult problems have been overcome in the past. The scientific community is now faced with the following problem: we have called attention to an activity which is potentially dangerous, and we are prepared to accept restraints. Yet elements of the public--including some scientists--have taken this publicly voiced concern of scientists as a signal to make the constraints much stronger, if not to prevent the work altogether. Unfortunately, the premise for this view is that if the scientists themselves are concerned, it must be more dangerous than they are willing to admit. This reaction may reflect the general distrust of authority that exists at the present time.

We must recognize that all major technological advances--the discovery of fire, the uses of metals, the vaccines against infectious diseases--always posed potential dangers. The process of gaining knowledge and of making choices is difficult and yet irreversible. Over-control in any area will stifle the development of much-needed further scientific and technological innovation. But let me say once more that we are obviously not supporting a laissez-faire attitude. A more subtle and sad result of the present excessive pressure and misunderstanding would be that, in the future, some other group of scientists who saw a potential danger--but not a clear and present danger--might be inhibited from speaking out.

What do we do now? A duly authorized and scientifically qualified committee of the National Institutes of Health worked long and hard to develop the set of guidelines for in vitro recombinant DNA work. Their agreements and disagreements are on the public record, as they should be. Therefore, I recommend that we unite behind their efforts, learn through time and experience if and how the guidelines ought to be modified. No set of guidelines can be perfect for they are made by men. I feel that we probably will be able to relax the guidelines as new, still unthought of, procedures develop. However, such procedures can be found only by further careful research. Above all we must sustain the active dialogue among all interested groups and do so in a spirit of mutual respect.

Thank you, I would be pleased to try to answer any questions you may have and to explain the scientific facts in more detail, if you wish.

TESTIMONY ON EXTENSION OF NIH GUIDELINES ON RECOMBINANT DNA RESEARCH TO ALL GOVERNMENTAL AND INDUSTRIAL PROGRAMS

SENATE SUBCOMMITTEE ON HEALTH

September 22, 1976 Halsted Holman, M.D.

The Asilomar conference began a process with far reaching consequences for science policy. The issue today concerns one aspect of that process, the extension of NIH guidelines covering the use of recombinant DNA to all governmental and industrial programs. In my view, present and future guidelines should apply to all groups using recombinant technology.

The current guidelines concern two technical approaches to safety issues raised by the present level of recombinant research, namely, laboratory precautions against escape of harmful recombinants and the use of "enfeebled" bacteria which would have difficulty surviving outside of an artificial laboratory environment. Few contend that either measure will provide certain safety; they are recognized as only minimizing danger. In particular there is considerable question about the stability and security of the enfeebled bacteria. To exempt any activity from such modest safeguards would be unconscionable. But extending the guidelines to all who enter the recombinant field is only a beginning.

Since Asilomar, the scope of the issues posed by recombinant research has begun to emerge. The guidelines pertain to only a small portion of the issues, which include:

1. The complexity and uncertainty of the involved scientific predictions.

2. The competing potentials for social benefit and harm inherent in recombinant technology.

3. The rights and responsibilities of individuals and institutions undertaking recombinant work.

4. The extent of public concern, and the difficulties in finding appropriate

mechanisms for public decisions concerning funding and regulation of the research, assessment of the consequences, and review of effectiveness of public policies.

5. Protection of the public and assignment of responsibility should harm occur.

Consideration of recombinant research policy has been enlivened by the emergence of significant self-interest on the part of many in the academic community, and the possibility of profound conflict of interest during the promulgation of the present guidelines and in the adoption of long term policies such as the granting of patents. Clearly, the issue is not purely one of scientific curiosity about nature. It strikes to the roots of man's use of knowledge as it affects society.

Despite the magnitude of the issues involved and the short time which has elapsed for their consideration, there has been great pressure to allow recombinant experimentation to continue. Why the haste? The most important reasons given are that the scientific quest for knowledge is a good in itself to which impediments are unjustified, and that substantial medical and agricultural benefits may result from the work. There are problems with both arguments. For example, modern science and technology have the power for great destruction and social disruption; recombinant research has that potential. No one has justified failure to weigh carefully in advance work with that potential. We have already had experience with an analogous situation: the assurances of some scientists and engineers that there was minimal harm in radioactive fallout before it was found to contain Strontium 90 and Iodine 131 stand as examples of the fallibility of "scientific" opinion. Good science, if anything, is prudent. It insists on careful controls and thorough understanding before it permits conclusions. Can we afford less from those involved in recombinant research and technology? Furthermore, it is by no means clear that the heralded medical and agricultural advances from recombinant technology will accrue. They are only possibilities. Each of the examples given for ameliorating disease or improving agricultural yield may be accomplished by other methods now being developed without analogous risks. Here too the experience with nuclear energy is illustrative. The promise of great benefit was the cornerstone of the defense of nuclear experimentation; it is now clear thirty years later that realizing that promise is at least problematical.

The issue of haste has other dimensions. First, recombinant research has yielded potential industrial technologies and thereby left the realm of intellectual curiosity for the profit market. The pending patent applications illustrate that transition. In this position, the research clearly demands careful weighing of costs and benefits. Second, new recombinant technologies will impart social power to their controllers; by doing so they assume profound social value. In this context, haste to pursue recombinant research and development before the issues they raise are identified and addressed serves to limit understanding and diminish prudence - the opposite of the initial justifications. When an activity reflects social values and possesses social consequences, decisions concerning its use should be made by public processes.

Industrial exploitation of recombinant technology magnifies the problems. Largescale processes will greatly increase chances of error and contamination of the environment with dangerous organisms. Industrial workers particularly will be at risk. Furthermore, industrial secrecy will hamper controls, impede the flow of knowledge crucial for safety, and deny public access to information essential for policy decisions. Secrecy is impermissible.

Since Asilomar there have been many important developments in public participation in science policy. They point the direction we should travel. There have been studies and by hearings by this Senate Committee, by the National Institutes of Health, and the National Commission for Protection of Human Subjects; the meeting at Airlie House called by Senators Kennedy and Javits; public hearings by the Cambridge City Council and by the University of Michigan; and a continuous debate in scientific and medical journals which has extended to the general press. Simultaneous considerations by the Presidential Panel on Biomendical Research have brought forth significant, alternative priorities for research, particularly from the Trade Union movement. The uses of nuclear energy and other aspects of environmental protection have received widespread public attention and action. These developments indicate wide interest and willingness to participate in the development of science policy on the part of many different constituencies. They/have also yielded important new perceptions and proposals which could extend and enrich the framework of science policy determination. While these developments do not yet constitute a cohesive whole, it is my impression that certain generalizations are widely supported. They are:

1. The integrity of the democratic process is at stake in modern science policy formulation, and the consent of the governed to actions undertaken within science and technology is of paramount importance.

2. The integrity of the scientific process and of professional services, including the development and use of knowledge, is dependent upon the integrity of the democratic process in determining priorities and policies.

3. There is critical public interest in the development and use of knowledge. Public competence and confidence in formulating science policy is urgently needed so that wise public contributions and assent to the purposes and practices of science may emerge.

I find these generalizations compelling. Yet this is a new arena for most of us. We do not yet know how best to turn the generalizations into practices. Therefore a period of experimentation is necessary in policy formulation, with many ideas receiving consideration and many forms being tested. In the immediate future, these activities should be our agenda. Haste in pursuit of recombinant DNA studies should be set aside while the search for the means of public participation in science policy is intensified.

In specific terms, I would propose:

1. Permanent constitution of the National Commission on Protection of Human Subjects with a mandate encompassing all aspects of science policy. This is an urgent need.

2. Convening by the Commission and other Federal agencies of regional meetings, particularly to include representatives of the universities, research institutions, industry and their surrounding communities, to consider science policy with particular reference to recombinant research.

3. National studies and hearings, convened by the Commission of Congress, to synthesize the results of regional and local activities, and to solicit additional proposals about priorities in research policy and mechanisms of public participation in policy formulation.

4. Particular attention to the issues of consent of those at risk from publicly mandated and supported research, and of civil liability for harm resulting therefrom.

5. Design of review mechanisms to evaluate and modify national science policies, including the guidelines on recombinant research, as experience is gained. Continuous interaction between policy and experience will yield the greatest public confidence and the best policy outcomes.

This is a full agenda. While it is unfolding there should be no relaxation of restrictions on recombinant research or fixing of attention primarily on that small aspect of the problem. Both science and the public interest will be served by guaranteeing that the issue is a public one, and assuring public authority over it.

Prepared Statement of Robert L. Sinsheimer

I would like to say that while, for reasons I will indicate, I believe the guidelines for recombinant DNA research are presently inadequate, they are certainly far better than no guidelines. They are intended to protect the public. I therefore support their extension to cover all research activity in this field, however supported and wherever performed. With respect to the specific question of the extension of the guidelines to industrial research activity, I would point out that this research does not require elaborate facilities and large capital investment. There is no reason to believe it will be limited to large pharmaceutical companies with proven records of care and reliability. Further, the virtual certainty of the development of new techniques and of the extension of these techniques to additional organisms and higher life forms will require a free flow of information, the continuing updating of guidelines and the continuing scrutiny of this field of research by a body which will endeavor to reflect the public interest.

As I have said I believe the guidelines, valuable as they are, are presently inadequate. I believe they do not provide sufficient recognition of the fact that we are here creating novel living organisms - unprecedented in the evolutionary order. As living organisms they are self-perpetuating and destined to their own individual evolution. I do not believe we can predict the properties of these organisms - created by the fusion of genes from disparate species - or their subsequent evolution, or their impact, present and future, on the existent biosphere. We do not know that there is a hazard here, but neither do we know there is not. If such hazard exist or develop, it will be, in this instance, uniquely irreversible. In these circumstances, I feel much more caution is appropriate than I find in the present guidelines.

Senator SCHWEIKER. Our next witness is Dr. Burke K. Zimmerman, Environmental Defense Fund.

We welcome you here.

STATEMENT OF BURKE K. ZIMMERMAN, PH. D., ENVIRONMENTAL DEFENSE FUND, WASHINGTON, D.C.

Dr. ZIMMERMAN. My name is Burke K. Zimmerman. I am a staff scientist with the Environmental Defense Fund here in Washington.

Senator SCHWEIKER. I know you have a detailed statement, which we will insert in the record at the conclusion of your testimony. You can give us a shortened version of it.

Dr. ZIMMERMAN. Yes.

I would like to discuss some of the main points I have made in my written testimony which have not really been dealt with by the witnesses so far this morning.

I have followed closely the deliberations at NIH in which the guidelines were developed. I gave testimony at the Advisory Committee meeting earlier this year in February.

My primary concern then, as now, concerns the fact that the guidelines developed by NIH have no authority whatsoever outside of NIH.

While we commend Dr. Fredrickson's efforts to ask for the compliance of the guidelines in the private sector, as well as Government agencies, I would like to discuss why I do not think this is going to work.

The second point of concern, and probably the most important issue that I think needs to be discussed here concerns the NIH guidelines, where no rigorous enforcement is proposed. Nor can any set of rules or safety procedures be really effective without enforcement. If indeed the potential for disaster is sufficiently great for NIH to have spent 2 years drafting safety guidelines and to have released an unprecedented environmental impact statement discussing the sorts of environmental and health problems believed to be possible as a result of these experiments, then there must be no room for error and no allowances made for those who may decide unilaterally that there is really no risk, or that other priorities are more important than voluntarily observing safety precautions.

The consensus among responsible scientists is that because we do not know all of the things that can happen, a potential risk must be assumed. There are, however, a minority of scientists who consider themselves so enlightened as to state unequivocally that there is absolutely no chance of anything untoward ever happening from the creation of organisms with an unprecedented genetic makeup. These individuals do so with no experimentally derived information to support their statements.

It is not only arrogant and presumptuous for any scientist to assume this attitude, but also irresponsible in view of even a potential for disaster.

Such dogmatic behavior would not be tolerated in any respectable scientific forum, and there is no reason that it should be taken seriously in any discussion of the hazards of recombinant DNA. If we are to err, let it be on the side of caution. For if it is otherwise, we may not be able to retrieve our mistakes once they are multiplying in the environment.

At the time the guidelines were released and put into effect, Dr. Donald Fredrickson, Director of NIH, called for the voluntary adoption of the guidelines by all other Federal agencies and by all privately supported institutions engaged in or supporting this type of research.

While the response from some quarters, such as the National Science Foundation, has been encouraging, that from other agencies has not been, such as the Department of Defense, which has, up to the time this testimony was prepared, been conspicuously silent.

And while some voices of praise for the guidelines have come from private industry, there has not yet been either endorsement of the guidelines nor the development of any alternative safety procedures.

The irony of the present state of affairs is thus, that the institutions and workers best qualified to perform recombinant DNA research and motivated by the noblest of scientific goals—the pursuit of knowledge—have gone to considerable trouble to police themselves. At the same time, those who would apply this knowledge toward less lofty ends—such as the development of biological weapons or the manufacture of a product to sell for profit—have neither agreed to comply with the collective wisdom of the best scientists in the field, as they could by endorsing and enforcing the NIH guidelines within their respective domains, nor have they developed a satisfactory alternative.

When the public health and the integrity of our environment are at stake, we cannot afford to accept excuses, such as the statement that to comply with certain features of the guidelines would violate industry's presumably sacred right to secrecy in a freely competitive market.

EDF contends that the public has a right to question not only the nature of the research programs proposed by any Government agency or private corporation, including both the imagined risks and benefits which may ensue, but the competence of those undertaking such research.

It is readily apparent that the Department of Defense is not interested in recombinant DNA research for purely altruistic motives or simply to satisfy the intellectual curiosity of its scientists. Similarly, the record of the drug companies in adequately testing their products for efficacy and safety and in openly and honestly reporting the results of those tests, has been severely criticized. Indeed, most of this past record has been exposed in hearings before this subcommittee. Why, then, should we assume that a technology such as recombinant DNA, which has the potential for much more far-reaching effects on the public health than the manufacture of ineffective or unsafe prescription drugs, will be more carefully developed and applied?

Should not the responsibility of the public which this research involves be required, fostered and enforced by an appropriate Government regulatory agency charged with the protection of public health?

It is the position of EDF that there must be a uniform and rigorously enforced set of safety procedures applicable to every laboratory in which these experiments are conducted regardless of who or what entity is paying for the research.

We contend that if science is indeed for the people, then not only do the results and discoveries of science belong to everyone, but science must be held accountable to the public for its actions.

Any area of science which poses a real or even a potential hazard to the public requires not only uniform safety practices essential but enforcement of these safety procedures. Perhaps some would consider it heretical for me, as a scientist, to be sitting here saying that scientists cannot be relied upon to do their work carefully, or to comply voluntarily with a set of rules. But I do so on the basis of some 14 years of research experience in which I have observed that there are perhaps some basic flaws in human nature which contribute more to man's behavior than his capacity to reason.

One of the major problems I have perceived in the apparent inability of many scientists and laymen to comprehend that a hazard exists if it does not impinge in some tangible or visible way on one of the five senses. If a hazardous agent cannot be seen, smelled, heard, felt, or tasted, then it is often difficult for many to take its presence seriously.

Infectious micro-organisms would be one such example. Radioactive materials and high energy ionizing radiation constitute a third class. And, to be sure, any hazardous materials created by recombinant DNA research will certainly constitute another class.

To give but one example, let us look back on our many years of experience with the way people have responded to the presence of radioactive materials in the laboratory, a subject with which I have had a great deal of firsthand experience. The handling of radioactive materials presents a known hazard for which there exists an elaborate mechanism to insure that human health is protected. Yet, in practice, it does not work. I think there is an important lesson to be learned here.

For as long as I can recall in 14 years of research, the purchase of any radioactive isotopes has required a license from the Atomic Energy Commission, and later from the Nuclear Regulatory Commission.

All institutions in which such materials are handled are required to have radiation safety officers whose responsibility it is to inspect all laboratories, provide any necessary safety equipment or shielding, provide containers for the proper disposal of radioactive wastes, monitor the laboratories for spills or any violations of the rigorous safety standards, provide fresh film badges for all personnel at frequent intervals, and generally to educate personnel in the proper handling of radioactive material.

The prime responsibility for laboratory workers, however, rests with the licensee, who is usually the principal investigator. This setup is not unlike the implementation of the guidelines for recombinant DNA research.

This all sounds very good on paper. In practice, however, while some radiation safety officers do indeed take their jobs seriously, and while many principal investigators do indeed thoroughly train their personnel and educate them as to the hazards inherent in radioactive materials, it is often the case that the safety procedures and their execution are a complete farce.

It is generally somewhat more difficult to obtain a driver's license than to obtain a license to purchase and use radioactive isotopes. One simply needs to fill out a form. At no time is it necessary to demonstrate any knowledge of the biological effects of ionizing radiation, any understanding of the physics of radioactive decay or of the effectiveness of materials in shielding various types of radiation, nor any knowledge of proper handling of materials or safety procedures.

But it is the responsibility of licensees to impart their expertise to those working under their supervision. But the abuses of radiation and radioactive materials in the laboratory, often committed by established scientists with impeccable credentials, are frequent. A couple of brief examples should suffice.

One of my colleagues at Johns Hopkins, who occupied the laboratory next to mine, and who holds an M.D., Ph. D., and who is now an assistant dean of Johns Hopkins Medical School, had, unknown to me, been working for several months with large quantities of the isotope iron-59, a short-lived emitter of rather energetic gamma rays.

I will not go into the adverse effect of gamma rays. I think you all have ideals of what they entail.

This fact was discovered when one of my more conscientious graduate students decided to clean up a small lab across the hall to see if there had been any radioactive contamination. To his surprise, the Geiger counter was off scale, not only at all points in the lab but over a significant part of the corridor outside.

He traced it to a large quantity of iron stored in a metal refrigerator next to the lab door, which was where my colleague stored each fresh shipment.

I was particularly concerned since his lab phone was mounted on the wall next to the door of his lab, situated perhaps 9 or 10 feet across the corridor from this rather intense course of radiation. Further, his technician, who was pregnant, used to spend at least an hour or two on the phone each day, and she would stretch the cord out into the hall to escape the noise of the lab, standing only a few feet away from her boss' stash of iron-59.

I brought the matter to his attention as tactfully as I could, and also alerted our radiation safety officer, who had never bothered to check whether or not my colleague had stored his material properly.

He subsequently apologized for his negligence and assured us all that he had corrected the problem by storing the iron-59 in his fume hood surrounded by a stack of lead bricks. That seemed to satisfy our radiation safety officer.

However, my graduate student was not satisfied, and he decided to make sure that there were no more such hazards. And he promptly found the Geiger counter off scale again, this time in our own lab.

It turned out that my colleague's fume hood was on the other side of the wall. He had put the isotope unshielded against the back wall of the hood and merely piled lead bricks in front and on top.

The flux of radiation through the back wall and beneath it was intense as ever. The radiation safety officer was summoned again, and my colleague advised of his error. This time the problem was finally corrected.

But, by this time, however, my colleague's technician and her unborn child had absorbed a considerable quantity of ionizing radiation.

Here was my colleague, who, in spite of his sophisticated training, had never bothered to really understand the nature of the isotope with which he had worked for many years. Thus we have a case where a rigorous set of safety procedures and licensing were completely ineffective because they relied on the voluntary compliance and knowledge of the scientists, and the competence of the safety officer.

And, unfortunately, this true story is not an isolated case. I have witnessed many similar incidents. In some cases there were accidents, but more often it was abuse and carelessness by well-trained people who knew or should have known better.

I cannot help but believe that if radiation made itself known—by its color, a sound, an odor, or if it could be felt—there would be far fewer cases of scientists dumping their liquid radioactive wastes down the drain because they are too lazy to walk to the waste container, and far fewer cases of simply not bothering to wear protective clothing or use proper shielding when handling large quantities of radioactive materials.

If it were not insidious, people would be more careful. But the attitude that "It will get the other guy but not me," prevails, too, and so does willful negligence.

On another occasion, a radiation safety officer told me, when I asked how he would suggest that I dispose of a rather large quantity of corrosive radioactive liquid, he said that he would not fill up the steel radioactive waste container with my material until the day it was to be picked up and carted off. That way, he said, by the time the liquid ate its way through the drums, they would be out of the State and would no longer be his responsibility.

I hope these anecdotes have effectively illustrated my point. That is, even when the hazard is understood, and a regulatory framework exists, it is far too idealistic and naive to assume that safety procedures will be properly executed, especially when the hazard or potential hazard cannot be seen, heard or smelled.

If I take such a pessimistic view of human nature, it is based on years of experience. People—some people, at least—will always be poorly informed or careless or downright cavalier. Thus, in order for any safety procedures to work effectively, there must be, as minimum requirements:

(a) Thorough education and training of all personnel—not simply the principal investigator—including demonstrated competence with any procedure entailing a hazard, and

(b) The rigorous monitoring and enforcement of safety procedures.

At this time, in view of the novelty of recombinant DNA research and the intensity of the debate over potential hazards, I would expect those laboratories now performing these experiments to be doing so with the utmost care. However, if recombinant DNA research is to become commonplace, proliferating to hundreds or thousands of laboratories, as has the use of radioactive isotopes, then I would expect both senior scientists and laboratory technicians—at least some of the people some of the time—to begin to drop their guard and to become less careful than they could be in always strictly observing a voluntary set of guidelines.

While the recombinant DNA guidelines themselves may or may not be an adequate set of safety procedures, I have serious doubts that the monitoring and enforcement procedures outlined in the NIH guidelines will be effective, given the experience of the fallability of human beings under similar circumstances.

Therefore, to repeat myself, not only must the guidelines or a similar set of safety procedures be required for all recombinant DNA research—it makes no sense to make rules which cover only a fraction of the research. But if they are to be effective, there must also be rigorous enforcement.

Senator SCHWEIKER. As we consider the implementation of these guidelines, I think the illustrations you have given make some very good points.

What specific recommendations or suggestions do you have in terms of the guidelines?

Dr. ZIMMERMAN. That is a very far-reaching question, and I think what we are going to have to do is at least insure that every person doing this kind of experiment or at least those labeled hazardous by some committee of experts must be thoroughly trained, perhaps obtain a Federal license, perhaps attend some training course given by the National Institutes of Health, but at least demonstrate their competence in safety procedures, and their competence to execute the safety procedures outlined in NIH guidelines at the very minimum.

There is still the question, of course, as to whether the guidelines themselves may be adequate. That has been mentioned here this morning. I am sure it will continue to be discussed.

One path that the Environmental Defense Fund is taking in order to see that the guidelines are implemented and the safety procedures are enforced is that we expect to file a petition within the next few days with the Secretary of Health, Education, and Welfare, in which we are requesting that he exercise the statutory authority vested in him under the Public Health Service Act to control the spread of communicable diseases.

In this case, our attorneys interpreted this to mean potential communicable disease, such as those that individuals fear could arise from recombinant DNA research.

Now, in order to do this, we are asking him to promulgate at once NIH guidelines as regulations governing all recombinant DNA research.

The petition also includes a request for public hearings on the substance of the NIH guidelines, including the broader issues of whether or not recombinant DNA research should be undertaken at all at this time and, if so, whether or not any strain of the colon bacillus E. coli can be considered a safe subject for these experiments. The petition concludes with the request that regulations governing recombinant DNA be ultimately based upon the proceedings of such a hearing.

If HEW is unresponsive to this question, then I see no alternative except extension of the guidelines by either legislation, or Executive order, or the bill that has been discussed here earlier, the Commission on Ethics in Biomedical Research on Human Subjects.

Your question is a very good one.

I think we have to consider the failings of human nature, the fact that no matter how strict a set of safety procedures appears on paper, that people will always make mistakes. Somehow there has to be some sort of system of checks and balances whereby laboratories are inspected periodically, and the contents examined periodically.

And as long as it is agreed there is sufficient potential hazard, such as we must if the NIH issues an unprecedented environmental impact statement, then we must assume that we must never relax our guard.

I really feel that without strict regulation and strict enforcement of those regulations, and especially if recombinant DNA research proliferates, then we may well find a lot of incidents such as those that I described with radioactive materials taking place.

Senator KENNEDY. I understand your testimony to say that guidelines are absolutely essential and that they may not be strenuous or strong enough to provide the kind of protections that you think are essential?

Dr. ZIMMERMAN. I am discussing particularly the parts on enforcement.

Senator KENNEDY. That is basically your position?

Dr. ZIMMERMAN. Yes, I would say so.

Senator KENNEDY. Thank you very much. I appreciate it.

Dr. ZIMMERMAN. Thank you.

[The prepared statement of Dr. Zimmerman follows:]

COMMENTS SUBMITTED IN TESTIMONY BEFORE THE SENATE HEALTH SUBCOMMITTEE HEARINGS ON RECOMBINANT DNA RESEARCH, SEPTEMBER 22, 1976

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My name is Burke K. Zimmerman, I live in McLean, Virginia and am at present a staff scientist with the Environmental Defense Fund ("EDF") in Washington, D. C. and a molecular biologist with the Radiation Biology Laboratory of the Smithsonian Institution, Rockville, Maryland. I received my A.B. in Chemistry and Physics from Harvard College in 1958 and my Ph.D. in Biophysics from Stanford University in 1962. Since that time, I have been involved in basic research in the molecular biology of DNA at the University of Chicago, Oak Ridge National Laboratory, Michigan State University and most recently as a member of the faculty of the Johns Hopkins University School of Medicine from 1969 to 1975.

Since joining EDF early this year, I have followed closely the deliberations at the National Institutes of Health in which the Guidelines for Research Involving Recombinant DNA Molecules were given final revision and approved. At the hearings of the Advisory Committee to the Director of NIH held in February, 1976, I submitted oral and written testimony on behalf of the Environmental Defense Fund.

Science has entered a completely unprecedented area of research. We simply don't know enough about the mechanism of genetic expression, or the gentic differences between a virulent and a benign microorganism or the etiology of cancer to be able to predict all of the properties of organisms containing recombinant DNA. The optimists predict that the technique will someday permit us to cure genetic diseases, and the pessimists warn of accidentally created Frankenstein-like monsters and global pandemics. In principle, probably anything that one can imagine is possible, but in the absence of data we may make only educated guesses at the probability of the occurrence of any hypothetical event. It is precisely this absence of data which has made this such a controversial subject. However, the majority of scientists agree that because we cannot predict what will happen and because the possibility of disaster must be assumed to exist however small the likelihood may be, until we have sufficient data to conclude otherwise, that we must venture cautiously into the unknown. It is to the credit and foresight of the scientists who, in 1974 called for a moratorium on recombinant DNA research until a set of safety guidelines could be developed. The result has been the commendable and monumental effort which has gone into the development of the National Institutes of Health ("NIH") guidelines, released on June 23, 1976.

There is still much disagreement among scientists as to whether or not the guidelines are adequate, too strict or too lenient. Hopefully the substantive issues of safety will be discussed in broad based public forums as an ongoing procedure as the guidelines are revised to accommodate new knowledge. However, it is not my purpose in appearing here today to discuss the merits of the guidelines themselves. My primary concern at the February NIH hearings, as now, is the lack of a set of uniform safety procedures governing recombinant DNA research outside of NIH.

Today, I would like to discuss why I believe that asking for voluntary compliance with the guidelines in other government agencies and private industry is not going to work. In order for the guidelines to be respected by all parties engaged in this novel branch of basic and applied research, and to be rigorously enforced they must have the strength of regulation of law.

If indeed the potential for disaster is sufficiently great for NIH to have spent two years drafting safety guidelines and to have released an unprecedented environmental impact statement discussing the sorts of environmental and health problems believed to be possible as a result of these experiments, then there must be no room for error and no allowances made for those who may decide unilaterally that there is really no risk, or that other priorities are more important than voluntarily observing safety precautions.

The consensus among responsible scientists is that because we don't know all of the things that can happen, a potential risk must be assumed. There are, however, a minority of scientists who consider themselves so enlightened as to state unequivocally that there is absolutely no chance of anything untoward ever happening from the creation of organisms with an unprecedented genetic make-up. These individuals do so with no experimentally derived information to support their statements. It is not only arrogant and presumptuous for any scientist to assume this attitude, but, also irresponsible in view of even a potential for disaster. Such dogmatic behavior would not be tolerated in any respectable scientific forum, and there is no reason that it should be taken seriously in any discussion of the hazards of recombinant DNA. If we are to err, let it be on the side of caution. For if it is otherwise, we may not be able to retrieve our mistakes once they are mutliplying in the environment.

At the time the guidelines were released and put into effect, Dr. Donald Frederickson, the director of NIH, called for the voluntary adoption of the guidelines by all other Federal agencies and by all privately supported institutions engaged in or supporting this type of research. While the response from some quarters, such as the National Science Foundation, has been encouraging, that from other agencies has not been, such as the Department of Defense, which has, up to the time this testimony was prepared, been conspicuously silent. And while some voices of praise for the guidelines have come from private industry, there has not yet been either endorsement of the guidelines nor the development of any alternative safety procedures.

The irony of the present state of affairs is thus, that the institutions and workers best qualified to perform recombinant DNA research and motivated by the noblest of scientific goals--the pursuit of knowledge--have gone to considerable trouble to police themselves. At the same time, those who would apply this knowledge toward less lofty ends--such as the development of biological weapons or the manufacture of a product to sell for profit--have neither agreed to comply with the collective wisdom of the best scientists in the field, as they could by endorsing and enforcing the NIH guidelines within their respective domains, nor have they developed a satisfactory alternative. When the public health and the integrity of our environment are at stake, we cannot afford to accept excuses, such as the statement that to comply with certain features of the guidelines would violate industry's presumably sacred right to secrecy in a freely competitive market.

EDF contends that the public has a right to question not only the nature of the research programs proposed by any government agency or private corporation including both the imagined risks and benefits which may ensue, but the competence of those undertaking such research. It is readily apparent that the Department of Defense is not interested in recombinant DNA research for purely altruistic motives or simply to satisfy the intellectual curiosity of its scientists. Similarly, the record of the drug companies in adequately testing their products for efficacy and safety and in openly and honestly reporting the results of those tests, has been severely criticized. Indeed, most of this past record has been exposed in hearings before this subcommittee. Why then should we assume that a technology such as recombinant DNA, which has the potential for much more far-reaching effects on the public health than the manufacture of ineffective or unsafe prescription drugs, will be more carefully developed and applied? Should not the responsibility to the public which this research involves be required, fostered and enforced by an appropriate government regulatory agency charged with the protection of public health?

It is the position of EDF that there must be a uniform and rigorously enforced set of safety procedures applicable to every laboratory in which these experiments are conducted regardless of who or what entity is paying for the research. We contend that if science is indeed for the people, then not only do the results and discoveries of science belong to everyone, but science must be held accountable to the public for its actions.

Any area of science which poses a real or even a potential hazard to the public requires not only uniform safety practices essential but enforcement of these safety procedures. Perhaps some would consider it heretical for me, as a scientist, to be sitting here saying that scientists cannot be relied upon to do their work carefully, or to comply voluntarily with a set of rules. But I do so on the basis of some fourteen years of research experience in which I have observed that there are perhaps some basic flaws in human nature which contribute more to man's behavior than his capacity to reason.

One of the major problems I have perceived is the apparent inability of many scientists and laymen to comprehend that a hazard exists if it does not impinge in some tangible or visible way on one of the five senses. If a hazardous agent cannot be seen, smelled, heard, felt, or tasted, then it is often difficult for many to take its presence seriously. Infectious micro-organisms would be one such example. Radioactive materials and high energy ionizing radiation constitute another class. Carcinogens in tobacco smoke, in the air we breathe or the water we drink may constitute a third class. And to be sure, any hazardous materials created by recombinant DNA research will certainly constitute another class. To give but one example, let us look back on our many years of experience with the way people have responded to the presence of radioactive materials in the laboratory, a subject with which I have had a great deal of first-hand experience. The handling of radioactive materials presents a known hazard for which there exists an elaborate mechanism to ensure that human health is protected. Yet, in practice it doesn't work. I think there is an important lesson to be learned here.

For as long as I can recall in fourteen years of research, the purchase of any radioactive isotopes has required a license from the Atomic Energy Commission, and later from the Nuclear Regulatory Commission. All institutions in which such materials are handled are required to have radiation safety officers whose responsibility it is to inspect all laboratories, provide any necessary safety equipment or shielding, provide containers for the proper disposal of radioactive wastes, monitor the laboratories for spills or any violations of the rigorous safety standards, provide fresh film badges for all personnel at frequent intervals, and generally to educate peronnel in the proper handling of radioactive material. The prime responsibility for laboratory workers, however, rests with the licensee, who is usually the principal investigator. This set-up is not unlike the implementation of the guidelines for recombinant DNA research.

This all sounds very good on paper. In practice, however, while some radiation safety officers do indeed take their jobs seriously, and while many principal investigators do indeed thoroughly train their personnel and educate them as to the hazards inherent in radioactive materials, it is often the case that the safety procedures and their execution are a complete farce.

It is generally somewhat more difficult to obtain a driver's license that to obtain a license to purchase and use radioactive isotopes. One simply needs to fill out a form. At no time is it necessary to demonstrate any knowledge of the biological effects of ionizing radiation, any understanding of the physics of radioactive decay or of the effectiveness of materials in shielding various types of radiation, nor any knowledge of proper handling of materials or safety procedures. But it is the responsibility of licensees to impart their expertise to those working under their supervision. But, the abuses of radiation and radioactive materials in the laboratory, often committed by established scientists with impeccable credentials, are frequent. A couple of brief examples should suffice.

One of my colleagues at Johns Hopkins, who occupied the laboratory next to mine, and who holds an M.D., Ph.D. and who is now an Assistant Dean of Johns Hopkins Medical School, had, unknown to me, been working for several months with large quantities of the isotope iron^{59}, a short-lived emitter of rather energetic gamma rays. This fact was discovered when one of my more conscientious graduate students decided to clean up a small lab across the hall to see if there had been any radioactive contamination. To his surprise, the Geiger counter was off scale, not only at all points in the lab but over a significant part of the corridor outside.

He traced it to a large quantity of iron^{59} stored in a metal refrigerator next to the lab door, which was where my colleague stored each fresh shipment. I was particularly concerned since his lab phone was mounted on the wall next to the door of his lab, situated perhaps 9 or 10 feet across the corridor from this rather intense source of radiation. Further, his technician, who was pregnant, used to spend at least an hour or two on the phone each day, and she would stretch the cord out into the hall to escape the noise of the lab, standing now only a few feet from her boss' stash of iron^{59}. I brought the matter to his attention as tactfully as I could and also alerted our radiation safety officer, who had never bothered to check whether or not my colleague had stored his material properly. He subsequently apologized for his negligence and assured us all that he had corrected the problem by storing the iron^{59} in his fume hood surrounded by a stack of lead bricks. That seemed to satisfy our radiation safety officer.

However, my graduate student was not satisfied and he decided to make sure that there were no more such hazards. And he promptly found the Geiger counter off scale again, this time in our own lab! It turned out that my colleague's fume hood was on the other side of the wall. He had put the isotope unshielded against the back wall of the hood and merely piled lead bricks in front and on top. The flux of radiation through the back wall and beneath it was intense as ever. The radiation safety officer was summoned again and my colleague advised of his error. This time the problem was finally corrected. But by this time, however, my colleague's technician and her unborn child had absorbed a considerable quantity of ionizing radiation.

Here was my colleague, who in spite of his sophisticated training, had never bothered to really understand the nature of the isotope with which he had worked for many years. Thus we have a case where a rigorous set of safety procedures and licensing were completely ineffective because they relied on the voluntary compliance and knowledge of the scientists, and the competence of the safety officer. And unfortunately, this true story is not an isolated case. I have witnessed many similar incidents. In some cases there were accidents, but more often it was abuse and carelessness by well-trained people who knew or should have known better.

I cannot help but believe that if radiation made itself known--by its color, a sound, an odor or if it could be felt--there would be far fewer cases of scientists dumping their liquid radioactive wastes down the drain because they are too lazy to walk to the waste container; and far fewer cases of simply not bothering to wear protective clothing or use proper shielding when handling large quantities of radioactive material. If it were not insidious, people would be more careful. But the attitude that -- "It will get the other guy but not me," prevails too, and so does willful negligence.

On another occasion, a radiation safety officer told me, when I asked how he would suggest that I dispose of a rather large quantity of corrosive radioactive liquid, he said that he wouldn't fill up the steel radioactive waste container with my material until the day it was to be picked up and carted off. That way, he said, by the time the liquid ate its way through the drums, they would be out of the state and would no longer be his responsibility.

I hope these anecdotes have effectively illustrated my point. That is, even when the hazard is understood, and a regulatory framework exists, it is far too idealistic and naive to assume that safety procedures will be properly executed, especially when the hazard or potential hazard cannot be seen, heard or smelled. If I take such a pessimistic view of human nature, it is based on years of experience. People--some people, at least--will always be poorly informed or careless or downright cavalier. Thus, in order for any safety procedures to work effectively there must be, as minimum requirements:

(a) Thorough education and training of all personnel (not simply the principal investigator) including demonstrated competence with any procedure entailing a hazard, and

(b) the rigorous monitoring and enforcement of safety procedures.

At this time, in view of the novelty of recombinant DNA research and the intensity of the debate over potential hazards, I would expect those laboratories now performing these experiments to be doing so with the utmost care. However, if recombinant DNA research is to become common place, proliferating to hundreds or thousands of laboratories, as has the use of radioactive isotopes, then I would expect both senior scientists and laboratory technicians---at least some of the people some of the time---to begin to drop their guard and to become less careful than they could be in always strictly observing a voluntary set of guidelines.

While the recombinant DNA guidelines themselves may or may not be an adequate set of safety procedures, I have serious doubts that the monitoring and enforcement procedures outlined in the NIH guidelines will be effective, given the experience of the fallability of human beings under similar circumstances. Therefore, to repeat myself, not only must the guidelines or a similar set of safety procedures be required for all recombinant DNA research--it makes no sense to make rules which cover only a fraction of the research, but, if they are to be effective, there must also be rigorous enforcement.

In an effort to achieve implementation of the ideas outlined above, the Environmental Defense Fund, together with the Natural Resources Defense Council, have prepared a petition which will be submitted shortly to the Secretary of Health, Education and Welfare in which he is requested to exercise the statutory authority vested in him under the Public Health Service Act to control the spread of communicable diseases--in this case even a potentially communicable disease--and to promulgate at once the NIH guidelines as regulations governing all recombinant DNA research. The petition also includes a request for public hearings on the substance of the NIH Guidelines including the broader issues of whether or not recombinant DNA research should be undertaken at all at this time, and, if so, whether or not any strain of the colon bacillus *E. coli* can be considered a safe subject for these experiments. The petition concludes with the request that regulations governing recombinant DNA be ultimately based upon the proceedings of such a hearing.

If HEW is unresponsive to this request then I see no alternative except extension of the guidelines by executive order or legislation, with the establishment of a workable means of enforcement.

Many scientists may consider this a hard line, especially for a fellow scientist to take. Some have expressed the fear that the Federal regulation of science in this way will limit the questions scientists may ask as well as the ways in which they may be answered. However, if we proceed rationally, and educate both the public and the lawmakers as to precisely what recombinant DNA research is all about, then we should be able to avoid public hysteria and an overreaction by Congress which could only result from misunderstanding. The scientists' freedom of inquiry need not be the price for ensuring the public safety.

Senator KENNEDY. Our last panel of witnesses consists of C. Joseph Stetler, president of the Pharmaceutical Manufacturers Association; Dr. John G. Adams, vice president, Scientific and Professional Relations; and Dr. Sidney Udenfriend, vice president and director of the Roche Institute of Molecular Biology.

I want to welcome you to the committee and look forward to your testimony.

I made some references during the course of the earlier part of our hearing the difficulties we have had at least with one major industry. However, we very much appreciate the fact that the PMA would come up with us and share its thoughts and feelings about this. I think it is a strong indication of the concerns being reflected within the industry.

That is, I find, very, very encouraging. We want to thank you very much for your willingness to respond and providing us with insight.

We look forward to your testimony.

STATEMENT OF C. JOSEPH STETLER, PRESIDENT, PHARMACEUTICAL MANUFACTURERS ASSOCIATION; JOHN G. ADAMS, Ph. D., VICE PRESIDENT, SCIENTIFIC AND PROFESSIONAL RELATIONS; AND SIDNEY UDENFRIEND, Ph. D., VICE PRESIDENT AND DIRECTOR OF THE ROCHE INSTITUTE OF MOLECULAR BIOLOGY, A PANEL

Mr. STETLER. Thank you, Senator.

Our testimony this morning will be brief, but we hope responsive to your inquiry into the subcommittee's inquiry into the involvement of PMA member firms in recombinant DNA research and our views on the guidelines recently published by the National Institutes of Health.

The subject of today's hearings is one which is recognized by all elements of the biomedical research community as a major breakthrough along the frontiers of science. As an institution engaged in biomedical research, the drug industry is acutely aware of its scientific, moral, and social responsibilities in this new field of research and development. It is for this reason that we are pleased to appear before your subcommittee and offer comments in support of a developing public policy that hopefully will maximize benefits and minimize risks.

We have attempted, in preparing for the hearings, to assess the extent of the activity of our member firms in this pioneering area. The responses revealed that all the major research-oriented pharmaceutical firms—about 30—are very much interested in it but that only a few are now actively engaged in recombinant DNA research, about five or six. It also appears that some of these firms are involved in such research as manufacturers of other than medicinal chemicals. We do not know the extent of their efforts in these other fields and we must, therefore, limit our comments to their activities in biomedical research.

In view of the technical nature of this subject, I would like to have Dr. Adams present the remainder of our statement and for him and Dr. Udenfriend to answer your questions. I am sure it will be clear from Dr. Adams' statement that the drug industry endorses the spirit and intent of the guidelines recently proposed by the National Institutes of Health.

With some minor modifications, which Dr. Adams will identify, it is our strong view that the drug industry should and will accept the guidelines as an affirmative and constructive approach.

Dr. Adams. Senator Kennedy, as you and the members of the subcommittee know, the prescription pharmaceutical industry is very heavily involved in general and biomedical research.

Our members have demonstrated a high level of sophistication in their research and development programs as their record of innovation and accomplishment clearly shows.

It is not surprising, therefore, that scientists in the drug industry are generally well aware of the pioneer work in DNA research which led to the discovery that DNA fragments bearing dissimilar but important genetic information could be recombined in a host cell to create hitherto unknown genetic species.

Industry scientists immediately recognized the potential applications of this new technology to many biological processes, particularly in the fields of medicine and agriculture, and more specifically in the production of important drugs from natural sources. It is also well recognized by scientists in the drug industry and elsewhere that there are potential risks inherent in this new technology and that great caution must be exercised in seeking its benefits for mankind.

We believe the drug industry has the proven scientific experience and capability to exercise that judgment.

Recombinant DNA research has been, and will continue to be, the subject of much debate on the question of balancing scientific freedom to pursue new avenues of research on the one hand, and the need for peer review and compliance with voluntary controls on the other. We believe that these two concepts are compatible and are accepted by responsible scientists and management in the drug industry and by other elements of the scientific community.

To this end, it is our opinion that a good start has been made in the "Guidelines for Research Involving Recombinant DNA Molecules," published in the Federal Register on July 7 by the National Institutes of Health.

As you may be aware, representatives of the drug industry took part in a meeting called by the Director of NIH on June 2 of this year. On that occasion, as the PMA spokesman, I said that our member firms would respond to the request for critical review of the guidelines and that immediate steps would be taken to convene a panel of experts for that purpose. That panel has since studied the question and, in addition, we have requested comments from all of our member firms for submission to the Director of the National Institutes of Health by the due date of November 1.

We commend the NIH for establishing guidelines and, particularly, for its efforts in seeking a consensus within the scientific community and from the public and private sectors. Research in this field holds great promise, and it is fair to expect that the same innovative genius which led to its discovery can also design systems to control it through peer review and physical and biological containment.

It is important to note that the drug industry is one of the most sophisticated scientific institutions engaged in the handling of biohazardous materials.

Some PMA member firms have long experience in working with pathogenic bacteria, viruses, Rickettsial and other pathogenic microbiological organisms. For example, the entire technology of vaccine research and production requires intimate knowledge of bacterial and viral genetics and is based on rigid adherence to appropriate levels of physical and biological containment.

Another example—the use of drug-resistant organisms to test new antibiotics and other chemotherapeutic agents against these strains of resistant pathogenic micro-organisms. Such research has led to the discovery of important new medicines. It has not resulted in any public health problems.

One further example of industry's experience and capability is the production of mutant strains of bacteria and other micro-organisms by X-ray and other mutagenic techniques in research designed to increase the yield of antibiotics and other drug substances produced by fermentation.

One must conclude from these examples and from the excellent safety record of the industry in research and production of other potentially biohazardous materials that it is well aware of the risks involved, and that it has the capability to avoid contamination or injury to its employees and to the environment.

For PMA's part, we will exert every effort to keep apprised of our member firms' involvement in such research, and will encourage cooperation with the scientific community and other peer groups, including Government agencies in adopting necessary controls.

It is too early to know the ultimate outcome of much of this research which has and will be undertaken. We might predict, however, that recombination of DNA in a host bacterial cell could produce quantities of medically needed natural products such as hormones and other important drugs by fermentation processes rather that by extraction of such raw materials as pancreas or other tissues of animals and plants.

Bacterial or other cultures of such recombinant DNA fragments could be maintained and propagated to serve as a constant and reliable source for production. New recombinant molecules might also serve as bases for new antibiotics or as a means to increase yields of existing antibiotics much in the same way now employed in the use of mutant strains.

The application of this technology to basic research of the disease process—more specifically to genetically induced or associated disease—offers great promise.

The potential risks of recombinant DNA research and its commercial application are well recognized. It is perhaps unfortunate that the term has become synonymous with "genetic engineering," a concept which is most frequently associated with the manipulation of human genetics or with the deliberate creation of highly toxic or virulent new species of plant and animal cells.

It is important, we believe, to emphasize that the present state of the art and the provisions of the NIH guidelines militate against research and development that would pose such a threat to society.

In the case of the drug industry, it is highly unlikely that research and development would involve organisms in classes 3, 4, and 5, as established by the Office of Biosafety of the Center for Disease Control of the U.S. Public Health Service in its publication entitled "Classification of Etiologic Agents on the Basis of Hazard," or that adequate biological containment procedures would not be available for EK–1 and EK–2 host vector systems.

Many of our member firms now routinely use P–1 and P–2 physical containment facilities in their research operations and it is not uncommon to find facilities in the drug industry that correspond very closely to the specifications for P–3 levels of containment. At least one of our firms is now engaged in constructing a P–4 facility.

There is little doubt then that the drug industry will be able to meet appropriate standards for physical and biological containment levels of recombinant DNA research and development.

In fact, a fail-safe system and a favorable benefit-risk ratio have already been established.

The PMA Expert Advisory Committee, which was convened in July, agrees that the spirit and intent of the NIH guidelines are quite acceptable. The panel further agrees that with some minor modifications, pharmaceutical firms would have few problems in applying the guidelines to their own research programs.

Based on responses to date to our request for comments and subject to these minor modifications which do not involve elements of risk or safety, it is fair to assume that PMA member firms will voluntarily comply with the guidelines.

In no instance was there any indication by our panel that the guidelines were inadequate to provide the necessary and desirable safeguards. Nor were there any reservations about industry's ability to comply with the proposed containment levels.

It was also the consensus of the panel that the creation of recombinant DNA Biohazard and/or Research Committees to review and approve research projects would pose no serious problem to industry and could be quickly implemented.

Review of the records of the meetings of such committees present no serious difficulty, except insofar as such minutes might involve proprietary or trade secret information. Such records should not necessarily be made public, but they could be made available to appropriate authorities where confidentiality could be guaranteed.

We do not view those features of the guidelines which might impinge on such intellectual property rights as insurmountable and trust that satisfactory modifications of the guidelines could be achieved.

The only other major concern of industry would be the restriction on volumes of greater than 10 liters. Such a restriction would be unrealistic in any scale-up operation for production purposes.

We recognize that the guidelines are primarily directed to small-scale research, but provision must be made for commercial application as technology expands and the state of the art changes.

As in the case of trade secrets and proprietary rights, we believe modifications or exceptions can accommodate this concern.

Thank you, Mr. Chairman. We will be pleased to respond to your questions.

Senator Kennedy. Thank you very much.

If we could go back in the testimony, Mr. Stetler, page 2, your first full paragraph:

> The responses revealed that all of the major research oriented pharmaceutical firms, about 30, are very much interested in it, but that only a few are now actively engaged in recombinant DNA research.

Do you know which firms are?

Mr. Stetler. Yes, I can give you the names of six that we know of, and two that are sort of tooling up, and have a capability.

Hoffmann-LaRoche, Upjohn, Lilly, Smith Kline, Miles. Pfizer and Abbott are not engaged, but are prepared to enter into the research.

Senator KENNEDY. Do you know the kind of research that is being done?

Mr. STETLER. I think we know of a couple projects that we can mention. We are not completely conversant, however, with all. We can give you some examples.

Dr. UDENFRIEND. I can give you one example, if I may.

Senator KENNEDY. I would be interested in the example, but more just really on the kind of conclusion, whether you do have knowledge or understanding, awareness of what the research is.

I think it would be interesting to hear what it is. However, I think knowing what the research is and knowing whether the guidelines are really applicable, are the key questions.

Mr. STETLER. I think we know pretty well. We do believe the guidelines are applicable and acceptable.

We did not really ask these companies, even the six specifically, what they were engaged in, in detail. We cannot answer that specifically.

Senator KENNEDY. Have the companies themselves, to your knowledge, been willing to accept the guidelines?

Mr. STETLER. Yes, very definitely.

Senator KENNEDY. Each of them?

Mr. STETLER. We have not had a negative response from any of them.

Senator KENNEDY. Have you had a positive response?

Mr. STETLER. Yes, positive response.

Senator KENNEDY. On each?

Mr. STETLER. Yes.

Mr. KENNEDY. Let me ask you this, since one of the real areas of concern that we have is the enforcement of these guidelines, how are we going to really make sure that we are going to have adequate compliance with the guidelines?

We have seen, even in terms of the regulatory agencies, the FDA and the Cancer Institute, in a more limited area, were unable to get that kind of compliance.

How are we going to do that, and would the firms welcome, or would they have reluctance to having some kind of review or monitoring of these guidelines?

Mr. STETLER. I think not. As we have talked, and listened to the discussion this morning, it seems to me one of the major problems—this extends well beyond our industry, to Government and academia—is to really know where this research is going on and by whom.

I think a possible answer before we get to a statute or regulations which would make the guidelines nonvoluntary, would be some mechanisms, either Executive order, or regulations, to establish a registry so that any of this research that is ongoing, whether it is industry, Government, or the academic community, would have to be reported and give at least some general indication as to the area of research and who is conducting it.

That would be at least a handle as to the extent of the research, where it was going on, and who is conducting it. The guidelines would still be applied, and could remain voluntary, at least at the outset.

Senator KENNEDY. That is an encouraging response. Let me ask, just further, in your testimony you say "it also appears that some of these firms are involved in such research as manufacturers of other than medicinal chemicals. We do not know the extent of their effort in these other fields, and we must, therefore, limit our comments to their activities in biomedical research."

Can you elaborate? Do you know the names of the firms, and do we know the nature of the work, and how do you suggest we find that out?

Mr. STETLER. Just a couple of for instances——

Senator KENNEDY. What is the magnitude?

Mr. STETLER. For instance, Eli-Lilly Co. is actively engaged in this type of research, which does have an application as far as agricultural chemicals are concerned. I think a couple of our other firms would be in that area.

We did not get as much detail from them in non-drug-related areas since we do not represent them in those fields. ButI think can say in view of their response to us, as far as prescription drugs are concerned, I would see no reason at all why they would not be just agreeable and willing to apply these guidelines to any category of research, other than medicinal chemicals.

Senator KENNEDY. Would there be other firms though that are not related, that you know about?

Mr. STETLER. I am sure there are other firms. As you said this morning, General Electric, firms in the petroleum industry and in the general area of chemical manufacturing, other than prescription drugs.

Senator KENNEDY. But in medicinal chemical area, would you know all the ones that are involved?

Mr. STETLER. I think so. I would say our membership firms produce 95 percent of the drugs and they must do 99 percent of the research; so that when we get a response, at least we have an idea of what prescription drug industry is doing.

Senator KENNEDY. What do you suggest we do with regard to those, Mr. Stetler?

Mr. STETLER. The only way I know really——

Senator KENNEDY. In the area of the medicinal chemicals, will your organization find out whether they are going to comply as well? Can you do that or not do it?

Mr. STETLER. We are really only in a position to discuss prescription drug industry with you, but we can, on that, say definitely they will.

Senator KENNEDY. Will you supply the names of the other ones in the medicinal chemical field?

Mr. STETLER. I shall to the extent that we have a handle on it. I would not pretend that the names would be all inclusive. We would be glad to give you what we can gather.

Senator KENNEDY. What is the organization that represents them?

Mr. STETLER. We represent 130 companies that manufacture——

Senator KENNEDY. No, that represent the medicinal chemicals.

Mr. STETLER. Manufacturing Chemists Association and there are two or three national trade associations that deal with chemical manufacturers.

Senator KENNEDY. I am informed by staff that we invited them to come here, and they said they are not authorized to speak on this.

Mr. STETLER. I think maybe they do not know which of their firms are involved because it is such a new area, but they certainly are authorized to speak.

Senator KENNEDY. Not on this issue they said, they were not authorized to speak.

We will get in touch with them again after this hearing, and send them a record, and ask them to speak to us on it.

Dr. ADAMS. We could respond in the case of our firms which have centralized research facilities conducting not only biomedical research, but possibly agricultural and other types of research.

Senator KENNEDY. That would be very helpful.

I think Mr. Stetler indicated that there was a positive response to it.

We will be in touch with that organization. We have the agricultural representative firms as well. They ought to be the ones that would speak.

Can you tell us about what volume of material you would need—this is on your last page, Dr. Adams—what volume are you talking about, when you say "volumes of greater than 10 liters?"

> The only other major concern of industry would be the restriction of volumes of greater than 10 liters.

What volumes are we talking about?

Dr. ADAMS. Let me reply in the negative by saying that the 10 liter quantity would not be adequate for pilot plant purposes.

The volumes would vary. If one were to scale up, given assurances of safety, I would assume that in a pilot plant scaleup, one might be talking in terms of 100, or 1,000, liters or even greater quantities.

There is no precise volume that can be specified.

Senator KENNEDY. What are the limits? What is the general range?

Dr. ADAMS. It would depend on the process, sir. At this moment it is almost impossible to answer.

Senator KENNEDY. What is the most it could be?

Dr. ADAMS. Let me put it in terms of gallons, 50 to 100 gallons, I would think, of a fermentation mix.

I would like to add, Senator Kennedy, that scaleup would never be undertaken until there was an absolute assurance of safety procedures, as evidenced by results in the research laboratory.

Dr. UNDENFRIEND. May I make a comment there?

There really is no division at that point between industry and academia, because somewhere along the line when scientists in academia has done their experiments over a number of years, he is going to want to scale up his preparation. There are large scale setups to do that for academic scientists today.

So the changing guidelines will automatically probably take that into account within several years.

Senator Kennedy. Do you have views on the appropriateness of the patent application?

Does it help or hinder industrial development?

Mr. Stetler. We just got, about a week ago, a letter from Dr. Frederickson on that question. We have referred the question to a patent committee. It is a little premature for me to comment on that.

But I am relatively sure, knowing our people, they will suggest that it will be appropriate to have patent rights, if the innovative work is conducted by industry.

I cannot see that that will prevent an organization from following the guidelines. I think they are really two separate issues.

I know there was a thought expressed today that there should be no patent rights. I think our position will be the opposite. But we do recognize it is a unique area of concern, and we will try to reflect that in the comments, and make that available to your committee.

It will be about a week.

Senator Kennedy. Now, as I understand, Mr. Stetler, the position of the association then is that although I suppose you cannot bind them in terms of the future the drug companies are going to conform with the guidelines?

Mr. Stetler. Correct.

Senator Kennedy. You would at least welcome any initiatives that would be developed in trying to find ways in which compliance can be worked out in terms of any of this research?

Mr. Stetler. A registry is necessary.

Senator Kennedy. And work with us, or at least an interagency group can work with us in that area, I think would be very helpful.

Mr. Stetler. Certainly.

Senator Kennedy. We will follow up with other associations as well.

I appreciate very much the testimony and the comments.

[The prepared statement of Mr. Stetler follows:]

STATEMENT ON RECOMBINANT DNA RESEARCH
ON BEHALF OF THE
PHARMACEUTICAL MANUFACTURERS ASSOCIATION
BEFORE THE
SENATE LABOR AND PUBLIC WELFARE COMMITTEE

SEPTEMBER 22, 1976

MR. CHAIRMAN AND MEMBERS OF THE COMMITTEE:

I AM C. JOSEPH STETLER, PRESIDENT OF THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION, AN ORGANIZATION COMPOSED OF 130 MEMBERS THAT DISCOVER, DEVELOP, MANUFACTURE AND MARKET MOST OF THE PRESCRIPTION DRUGS AND A LARGE PERCENTAGE OF THE DIAGNOSTIC REAGENTS AND MEDICAL DEVICES AVAILABLE IN THE UNITED STATES. ACCOMPANYING ME ARE DR. JOHN G. ADAMS, PMA VICE PRESIDENT, SCIENTIFIC AND PROFESSIONAL RELATIONS AND DR. SIDNEY UDENFRIEND, VICE PRESIDENT AND DIRECTOR OF THE ROCHE INSTITUTE OF MOLECULAR BIOLOGY.

OUR TESTIMONY WILL BE BRIEF, BUT WE HOPE RESPONSIVE TO THE SUBCOMMITTEE'S INQUIRY INTO THE INVOLVEMENT OF PMA MEMBER FIRMS IN RECOMBINANT DNA RESEARCH AND OUR VIEWS ON THE GUIDELINES RECENTLY PUBLISHED BY THE NATIONAL INSTITUTES OF HEALTH.

THE SUBJECT OF TODAY'S HEARINGS IS ONE WHICH IS RECOGNIZED BY ALL ELEMENTS OF THE BIOMEDICAL RESEARCH COMMUNITY AS A MAJOR BREAKTHROUGH ALONG THE FRONTIERS OF SCIENCE. AS AN INSTITUTION ENGAGED IN BIOMEDICAL RESEARCH, THE DRUG INDUSTRY IS ACUTELY AWARE OF ITS SCIENTIFIC, MORAL AND SOCIAL RESPONSIBILITIES IN THIS NEW FIELD

OF RESEARCH AND DEVELOPMENT. IT IS FOR THIS REASON THAT WE ARE PLEASED TO APPEAR BEFORE YOUR SUBCOMMITTEE AND OFFER COMMENTS IN SUPPORT OF A DEVELOPING PUBLIC POLICY THAT HOPEFULLY WILL MAXIMIZE BENEFITS AND MINIMIZE RISKS.

WE HAVE ATTEMPTED, IN PREPARING FOR THE HEARINGS, TO ASSESS THE EXTENT OF THE ACTIVITY OF OUR MEMBER FIRMS IN THIS PIONEERING AREA. THE RESPONSES REVEALED THAT ALL OF THE MAJOR RESEARCH-ORIENTED PHARMACEUTICAL FIRMS (ABOUT 30) ARE VERY MUCH INTERESTED IN IT BUT THAT ONLY A FEW ARE NOW ACTIVELY ENGAGED IN RECOMBINANT DNA RESEARCH. IT ALSO APPEARS THAT SOME OF THESE FIRMS ARE INVOLVED IN SUCH RESEARCH AS MANUFACTURERS OF OTHER THAN MEDICINAL CHEMICALS. WE DO NOT KNOW THE EXTENT OF THEIR EFFORTS IN THESE OTHER FIELDS AND WE MUST, THEREFORE, LIMIT OUR COMMENTS TO THEIR ACTIVITIES IN BIOMEDICAL RESEARCH.

IN VIEW OF THE TECHNICAL NATURE OF THIS SUBJECT, I WOULD LIKE TO HAVE DR. ADAMS PRESENT THE REMAINDER OF OUR STATEMENT AND FOR HIM AND DR. UDENFRIEND TO ANSWER YOUR QUESTIONS. I AM SURE IT WILL BE CLEAR FROM DR. ADAMS' STATEMENT THAT THE DRUG INDUSTRY ENDORSES THE SPIRIT AND INTENT OF THE GUIDELINES RECENTLY PROPOSED BY THE NATIONAL INSTITUTES OF HEALTH. WITH SOME MINOR MODIFICATIONS, WHICH DR. ADAMS WILL IDENTIFY, IT IS OUR OPINION THAT THE DRUG INDUSTRY SHOULD AND WILL ACCEPT THE GUIDELINES AS AN AFFIRMATIVE AND CONSTRUCTIVE APPROACH.

STATEMENT BY DR. JOHN G. ADAMS

MR. CHAIRMAN:

AS YOU AND THE MEMBERS OF THE SUBCOMMITTEE KNOW, THE PRESCRIPTION PHARMACEUTICAL INDUSTRY IS VERY HEAVILY INVOLVED IN GENERAL AND BIOMEDICAL RESEARCH. OUR MEMBER FIRMS HAVE DEMONSTRATED A HIGH

LEVEL OF SOPHISTICATION IN THEIR RESEARCH AND DEVELOPMENT PROGRAMS AS THEIR RECORD OF INNOVATION AND ACCOMPLISHMENT CLEARLY SHOWS. IT IS NOT SURPRISING, THEREFORE, THAT SCIENTISTS IN THE DRUG INDUSTRY ARE GENERALLY WELL AWARE OF THE PIONEER WORK IN DNA RESEARCH WHICH LED TO THE DISCOVERY THAT DNA FRAGMENTS BEARING DISSIMILAR BUT IMPORTANT GENETIC INFORMATION, COULD BE RECOMBINED IN A HOST CELL TO CREATE HITHERTO UNKNOWN GENETIC SPECIES.

INDUSTRY SCIENTISTS IMMEDIATELY RECOGNIZED THE POTENTIAL APPLICATIONS OF THIS NEW TECHNOLOGY TO MANY BIOLOGICAL PROCESSES, PARTICULARLY IN THE FIELDS OF MEDICINE AND AGRICULTURE, AND MORE SPECIFICALLY IN THE PRODUCTION OF IMPORTANT DRUGS FROM NATURAL SOURCES. IT IS ALSO WELL RECOGNIZED BY SCIENTISTS IN THE DRUG INDUSTRY AND ELSEWHERE THAT THERE ARE POTENTIAL RISKS INHERENT IN THIS NEW TECHNOLOGY AND THAT GREAT CAUTION MUST BE EXERCISED IN SEEKING ITS BENEFITS FOR MANKIND. WE BELIEVE THE DRUG INDUSTRY HAS THE PROVEN SCIENTIFIC EXPERIENCE AND CAPABILITY TO EXERCISE THAT JUDGMENT.

RECOMBINANT DNA RESEARCH HAS BEEN, AND WILL CONTINUE TO BE, THE SUBJECT OF MUCH DEBATE ON THE QUESTION OF BALANCING SCIENTIFIC FREEDOM TO PURSUE NEW AVENUES OF RESEARCH ON THE ONE HAND, AND THE NEED FOR PEER REVIEW AND COMPLIANCE WITH VOLUNTARY CONTROLS ON THE OTHER. WE BELIEVE THAT THESE TWO CONCEPTS ARE COMPATIBLE AND ARE ACCEPTED BY RESPONSIBLE SCIENTISTS AND MANAGEMENT IN THE DRUG INDUSTRY AND BY OTHER ELEMENTS OF THE SCIENTIFIC COMMUNITY. TO THIS END, IT IS OUR OPINION THAT A GOOD START HAS BEEN MADE IN THE "GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES", PUBLISHED IN THE FEDERAL REGISTER ON JULY 7 BY THE NATIONAL INSTITUTES OF HEALTH.

As you may be aware, representatives of the drug industry took part in a meeting called by the Director of NIH on June 2 of this year. On that occasion, as the PMA spokesman, I said that our member firms would respond to the request for critical review of the Guidelines and that immediate steps would be taken to convene a panel of experts for that purpose. That panel has since studied the question, and, in addition, we have requested comments from all of our member firms for submission to the Director of the National Institutes of Health by the due date of November 1.

We commend the NIH for establishing Guidelines and, particularly, for its efforts in seeking a consensus within the scientific community and from the public and private sectors. Research in this field holds great promise, and it is fair to expect that the same innovative genius which led to its discovery can also design systems to control it through peer review and physical and biological containment.

It is important to note that the drug industry is one of the most sophisticated scientific institutions engaged in the handling of biohazardous materials. Some PMA member firms have long experience in working with pathogenic bacteria, viruses, Rickettsial and other pathogenic microbiological organisms. For example, the entire technology of vaccine research and production requires intimate knowledge of bacterial and viral genetics and is based on rigid adherence to appropriate levels of physical and biological containment.

Another example -- the use of drug-resistant organisms to test new antibiotics and other chemotherapeutic agents against these strains of pathogenic microorganisms. Such research has led to the

DISCOVERY OF IMPORTANT NEW MEDICINES. IT HAS NOT RESULTED IN ANY PUBLIC HEALTH PROBLEMS.

ONE FURTHER EXAMPLE OF INDUSTRY'S EXPERIENCE AND CAPABILITY IS THE PRODUCTION OF MUTANT STRAINS OF BACTERIA AND OTHER MICROORGANISMS BY X-RAY AND OTHER MUTAGENIC TECHNIQUES IN RESEARCH DESIGNED TO INCREASE THE YIELD OF ANTIBIOTICS AND OTHER DRUG SUBSTANCES PRODUCED BY FERMENTATION.

ONE MUST CONCLUDE FROM THESE EXAMPLES AND FROM THE EXCELLENT SAFETY RECORD OF THE INDUSTRY IN RESEARCH AND PRODUCTION OF OTHER POTENTIALLY BIOHAZARDOUS MATERIALS THAT IT IS WELL AWARE OF THE RISKS INVOLVED, AND THAT IT HAS THE CAPABILITY TO AVOID CONTAMINATION OR INJURY TO ITS EMPLOYEES AND TO THE ENVIRONMENT. FOR PMA'S PART, WE WILL EXERT EVERY EFFORT TO KEEP APPRISED OF OUR MEMBER FIRMS' INVOLVEMENT IN SUCH RESEARCH, AND WILL ENCOURAGE COOPERATION WITH THE SCIENTIFIC COMMUNITY AND OTHER PEER GROUPS, INCLUDING GOVERNMENT AGENCIES IN ADOPTING NECESSARY CONTROLS.

IT IS TOO EARLY TO KNOW THE ULTIMATE OUTCOME OF MUCH OF THIS RESEARCH WHICH HAS AND WILL BE UNDERTAKEN. WE MIGHT PREDICT, HOWEVER, THAT RECOMBINATION OF DNA IN A HOST BACTERIAL CELL COULD PRODUCE QUANTITIES OF MEDICALLY NEEDED NATURAL PRODUCTS SUCH AS HORMONES AND OTHER IMPORTANT DRUGS BY FERMENTATION PROCESSES RATHER THAT BY EXTRACTION OF SUCH RAW MATERIALS AS PANCREAS OR OTHER TISSUES OF ANIMALS AND PLANTS.

BACTERIAL OR OTHER CULTURES OF SUCH RECOMBINANT DNA FRAGMENTS COULD BE MAINTAINED AND PROPAGATED TO SERVE AS A CONSTANT AND RELIABLE SOURCE FOR PRODUCTION. NEW RECOMBINANT MOLECULES MIGHT ALSO SERVE AS BASES FOR NEW ANTIBIOTICS OR AS A MEANS TO INCREASE

YIELDS OF EXISTING ANTIBIOTICS MUCH IN THE SAME WAY NOW EMPLOYED IN THE USE OF MUTANT STRAINS. THE APPLICATION OF THIS TECHNOLOGY TO BASIC RESEARCH OF THE DISEASE PROCESS - MORE SPECIFICALLY TO GENETICALLY INDUCED OR ASSOCIATED DISEASE - OFFERS GREAT PROMISE.

THE POTENTIAL RISKS OF RECOMBINANT DNA RESEARCH AND ITS COMMERCIAL APPLICATION ARE WELL RECOGNIZED. IT IS PERHAPS UNFORTUNATE THAT THE TERM HAS BECOME SYNONYMOUS WITH "GENETIC ENGINEERING", A CONCEPT WHICH IS MOST FREQUENTLY ASSOCIATED WITH THE MANIPULATION OF HUMAN GENETICS OR WITH THE DELIBERATE CREATION OF HIGHLY TOXIC OR VIRULENT NEW SPECIES OF PLANT AND ANIMAL CELLS. IT IS IMPORTANT, WE BELIEVE, TO EMPHASIZE THAT THE PRESENT STATE OF THE ART AND THE PROVISIONS OF THE NIH GUIDELINES MILITATE AGAINST RESEARCH AND DEVELOPMENT THAT WOULD POSE SUCH A THREAT TO SOCIETY.

IN THE CASE OF THE DRUG INDUSTRY, IT IS HIGHLY UNLIKELY THAT RESEARCH AND DEVELOPMENT WOULD INVOLVE ORGANISMS IN CLASSES 3, 4 AND 5 AS ESTABLISHED BY THE OFFICE OF BIOSAFETY OF THE CENTER FOR DISEASE CONTROL OF THE U. S. PUBLIC HEALTH SERVICE IN ITS PUBLICATION ENTITLED "CLASSIFICATION OF ETIOLOGIC AGENTS ON THE BASIS OF HAZARD" OR THAT ADEQUATE BIOLOGICAL CONTAINMENT PROCEDURES WOULD NOT BE AVAILABLE FOR EK-1 AND EK-2 HOST VECTOR SYSTEMS. MANY OF OUR MEMBER FIRMS NOW ROUTINELY USE P-1 AND P-2 PHYSICAL CONTAINMENT FACILITIES IN THEIR RESEARCH OPERATIONS AND IT IS NOT UNCOMMON TO FIND FACILITIES IN THE DRUG INDUSTRY THAT CORRESPOND VERY CLOSELY TO THE SPECIFICATIONS FOR P-3 LEVELS OF CONTAINMENT. AT LEAST ONE OF OUR FIRMS IS NOW CONSTRUCTING A P-4 FACILITY.

There is little doubt then that the drug industry will be able to meet appropriate standards for physical and biological containment levels of recombinant DNA research and development. In fact, a fail-safe system and a favorable benefit-risk ratio have already been established.

The PMA Expert Advisory Committee, which was convened in July agrees that the spirit and intent of the NIH Guidelines are quite acceptable. The Panel further agrees that with some minor modifications, pharmaceutical firms would have few problems in applying the Guidelines to their own research programs. Based on responses to date to our request for comments and subject to these minor modifications which do not involve elements of risk or safety, it is fair to assume that PMA member firms will voluntarily comply with the Guidelines.

In no instance was there any indication by our panel that the Guidelines were inadequate to provide the necessary and desirable safeguards. Nor were there any reservations about industry's ability to comply with the proposed containment levels. It was also the consensus of the panel that the creation of Recombinant DNA Biohazard and/or Research Committees to review and approve research projects would pose no serious problem to industry and could be quickly implemented. Review of the records of the meetings of such Committees present no serious difficulty, except insofar as such minutes might involve proprietary or trade secret information. Such records should not necessarily be made public, but they could be made available to appropriate authorities where confidentiality could be guaranteed. We do not view those features of the Guidelines which might impinge on such intellectual property rights as insurmountable and trust that satisfactory modifictions to the Guidelines could be achieved.

The only other major concern of industry would be the restriction on volumes of greater than ten liters. Such a restriction would be unrealistic in any scale-up operation for production purposes. We recognize that the Guidelines are primarily directed to small-scale research but provision must be made for commercial application as technology expands and the state of the art changes. As in the case of trade secrets and proprietary rights, we believe modifications or exceptions can accommodate this concern.

Thank you, Mr. Chairman. We will be pleased to respond to your questions.

Senator KENNEDY. I think we have seen as a result of the hearings during the course of this morning that it is an enormous area of uncertainty surrounding this whole area of recombinant DNA research.

No one can predict with any degree of absolute certainty what the dangers would be, or what the opportunities and advantages would be.

I think when some of our most skilled and talented and thoughtful scientists and researchers point out the dangers, they spell out a really living holocaust for this Nation and country and the world, and when they use their minds to elaborate on the possibilities in terms of using it to the benefit of mankind, they are really virtually unlimited.

As has been pointed out today by people who really should know, and do know the significance in terms of the whole research area, the whole process of what we are talking about in terms of its implications on mankind is as easily important, if not more important than the splitting of the atom and all the implications that that has had in the world.

Therefore, the efforts which have been promulgated by the National Institutes of Health seem to me to offer at least initially the best opportunity by which any efforts, or any research must be guided by.

We heard the testimony this morning, and read about this subject matter, and realize those guidelines should in no way be thought to be fixed in concrete. They should be adjusted, changed, altered, as the situation requires. They should be strengthened, to the extent that dangers and new dangers are presented. They should be lifted as the concerns for safety are eased.

Therefore, it is extremely important that we have a continuing and ongoing review of these guidelines. Even once we have established these guidelines, we have seen from our recent past the importance of compliance with them.

The record of various governmental agencies over the history, particularly the recent past, and the work that this committee has done in a number of areas has not been reassuring.

Therefore, this committee is going to assume a very significant part of its responsibility insuring that those that do have responsibility in Government are going to insure compliance with those regulations, and we are going to monitor that very, very closely over the period of the future.

We are encouraged by the administration's willingness to insure that the Department of Defense is going to comply.

We are troubled by the apparent failure of the sense of urgency, I think, quite frankly, by the Executive, in assuring that those NIH regulations are going to be applicable to all governmental contracting and research.

I think it is unjustified and inexcusable that it has not done so today.

I believe that Dr. Fredrickson with his sense of urgency, believes it should be done. He stated that. We are hopeful of working together—Senator Javits, myself, Senator Schweiker, the members of the committee—to urge immediate kind of assurance that this is going to be covered.

We are heartened by the fact that the Pharmaceutical Manufacturers Association has indicated a commitment to support those guidelines. That is reassuring.

We welcome their comments today.

We are distressed by the fact that some, both associations, organizations, and industry, have not focused on this. This is a charitable way of viewing their response to our inquiries.

Others have clearly demonstrated the kind of concern which I think is absolutely essential if we are going to really provide the types of protections for the American people.

We are going to press with the various associations with industry to assure the protections have compliance with these guidelines.

Finally, I think it is absolutely essential that the public be brought into this process. I think if there is a continuing echo from the course of these hearings this morning it is the importance of the public's being informed about this particular issue, understanding the potential hazards and benefits.

I believe that they are fully competent to try and sift through the complexities of the potential dangers and potential hazards.

It is laid out to them in the kind of way of constructing a positive presentation, I think that this will really ease the dangers of demagoguery on this kind of issue, the scare and frightening tactics which have been the case in some other extremely important issues of public concern.

I am very hopeful that we can develop with the scientific community the process and the forum and the means by which the public generally across the country can be made aware of this issue, and specifically in those areas where this process, this research, is going to take place, that they can be involved in having an input in it the way the people of Cambridge, Mass., have had in our situation.

I think we have seen in the recent articles from the New York Times magazine, which has been made a part of the record, where it said:

> In the course of 25 years of Army research on biological warfare agents at Fort Dietrich, equipped with the highest level of physical containment facilities, there were 423 accidental infections, and three deaths. Accidents due to human error are inevitable, all the more so because scientists under pressure become inured to taking risks. The temptation to do things the easy, quick way, instead of the safe way is hard to resist.

The dangers are significant. The benefits obviously are virtually unlimited. But we want to insure that we proceed in a way which is going to provide adequate safety for the American people, and still the opportunity for continued progress in an area which it does offer a sense of hope for the American future.

I want to thank those who participated in our hearing this morning.

We will continue our interest and our oversight in this extremely important area of public policy.

Thank you very much.

At this point we will include in the record additional pertinent material submitted by interested parties unable to be present at this hearing.

[The following material was subsequently supplied for the record:]

James I. Mangi, Ph.D.

21 Sep 76

Sen. Edward Kennedy
Senate R 4228
Dirksen Bldg

Dear Senator Kennedy:

I understand that your Senate Committee is to hold hearings on the subject of Recombinant DNA research. I request that the enclosed statement be submitted to your committee as part of its record. Thank you very much.

Sincerely,
James I. Mangi
James I. Mangi
NY Ocean Science Lab
Montauk, NY 11954

James I. Mangi, Ph.D.

I hold a Ph.D. in Biology; my field is the study of algae, so I have no direct involvement with recombinant DNA research. As a scientist, I wish to contribute some thoughts on the roles of the citizen and the scientist in this controversy.

In the history of this issue, from the 1974 call for a moratorium (Berg et al 1974, Science 185:303), to the promulgation of formal guidelines (NIH, 23 June 1976) to the continuing commentary on the subject (Chargaff 1976, Science 192:938; Dyson 1976, Science 193:6; Hubbard 1976,Science 193:836), I detect an arrogance on the part of much of the scientific community. This arrogance seems to assume that scientists know better, that anything scientists can do, is worth doing, and it should be done as quickly as possible.

These tacit assumptions are products of the attitude that scientists are apart from ordinary society. These priests of Science seem to expect society to support them, yet feel no obligation to the somehow pagan layperson. Expressed in another way, some scientists are les enfants terribles of society. They condescendingly accept the praise for the past and future achievements of science, but will brook no opposition or criticism.

As a scientist, I feel that this orientation is very wrong and that the public, and its representatives should help correct it. Better science education is one aspect of the solution, but more immediately, people should acquire the habit of challenging scientists.

When a segment of the scientific community protests, "Who are you to challenge our judgment?" (e.g. in drawing up the guidelines for DNA research), citizens should adopt the attitude that they are the society which supports the scientists, the society to whose needs science must be responsive. Scientists are a part of society, not apart from it.

Protests over restriction of freedom of enquiry should be met with the attitude that all freedoms involve responsibilities. Science has traditionally been granted wide, but not absolute freedom. If ambitious scientists do not live up to their responsibilities for public and environmental safety, then the public, through its representatives ought to act to insure those responsibilities are met.

The arguments for and against recombinant DNA involve mostly educated guesswork, although a great deal depends on the decisions made. It is largely a matter of which fiction you choose to believe: the wondrous benefits which could someday accrue, or the horrid calamities which could befall us. The record of science fictions which have become science facts teaches us that one or the other scenario, or both, will very likely come to pass.

I feel that the risks involved demand even greater caution- in the form of tighter guidelines, restriction of this research to very few facilities and delay until safer experimental techniques are available.

I feel that the prescribed containment precautions will not adequately guard against human error, especially if the humans are involved in a highly competitive race for fame. Indeed, safety precautions for dangerous research do fail: infectious agents have escaped from highly sophisticated labs in the U.S. and in England; the early polio vaccine received by many people, was contaminated with virus; farm animals have died from the escape of nerve gas from the Army's proving ground near Dugway, Utah.

With a proliferation of DNA research would come a proliferation of human error, and a proliferation of escapes of genetically altered bacteria and viruses. In the light of the mystery of the Legionnaires' disease, is it not over-confident to assert that any such escapees will be without harm to any segment of the ecosystem?

Yet many scientists are impatient to get on with this work. Why? What is the hurry? The cost of delay is that our ignorance of secrets of the gene will persist awhile longer. The cost of reckless research may be immense, irreparable damage, not to the researcher, bût to large segemtns of the natural world.

It would be bitterly ironic if, in the name of helping humanity, our scientists unleashed a new Black Plague. It is worth considering that diseases such as many forms of cancer, which are inflicted on humanity by humanity, are proving harder to combat than diseases caused by lesser organisms. We should not take a chance on adding another set of human-induced pathogens into the world. We ought to heed the wisdom of the words of Pogo: "We have met the enemy, and he is us."

SEEKING WISDOM IN RECOMBINANT DNA RESEARCH

BY

Paul Berg, Department of Biochemistry, Stanford University Medical
Center, Stanford, California 94305

Maxine Singer, National Cancer Institute, National Institutes of Health,
Bethesda, Maryland 20014

Robert Sinsheimer, the eminent American biologist at the California Institute of Technology, has challenged scientists and the public to couple wisdom to the pursuit of knowledge; he appeals, particularly, for wisdom in the conduct of recombinant DNA research. Sinsheimer's outstanding scientific accomplishments and his consistent attention to the impact of scientific advances on society, compel us to consider his concerns and warnings carefully. Indeed, people of conscience do not quarrel with Sinsheimer's eloquent plea for wisdom, for each of us yearns to achieve a wise and responsible resolution of this matter. However, what confounds us is not whether wisdom should prevail, but to identify the wisest course to follow.

Sinsheimer, along with many knowledgeable scientists and laymen, recognizes that recombinant DNA research portends exciting and momentous advances for science and society. The new found ability -- to dissect the chromosomes of higher organisms and to obtain large quantities of individual genetic elements in pure form -- eliminates a major barrier to solving the molecular details of gene structure and function. Important advances in this field are taking place today and as research moves ahead our knowledge of the genetic chemistry of higher organisms will increase dramatically. This knowledge will expand our understanding of all living systems and help clarify the nature of health and disease; in time we can expect rational rather than empirical approaches to disease prevention and cure. The promise of recombinant DNA research is not limited to medicine; opportunities for practical application to industrial and agricultural problems will follow as well. The sweeping charge by some critics, that the anticipated benefits of this research are dubious and speculative, is misleading and simplistic: It ignores the human urge to understand both our own nature and the world that surrounds us and it denies the need to acquire fresh insights if we are to ameliorate the individual and societal tragedies caused by disease.

Simultaneously with the development of techniques for recombining and propagating hybrid DNAs, scientists expressed concern that new and potentially dangerous organisms might inadvertently be produced and threaten man and his environment if they were to escape the laboratory. Much has been done to eliminate or reduce the risk of such an unacceptable outcome. But Sinsheimer continues to express grave concern that recombinant DNA research will be done carelessly. He also imagines another fearful hazard: recombinant DNA experiments would initiate genetic intercourse between, for example, bacterial and animal cells and thereby breach the "natural barrier" that, he postulates, has evolved to separate the two forms of life. If this were to occur, Sinsheimer warns, it would alter evolution in unpredictable ways. No scientific fact or theory predicts or supports the existence of such a barrier, nor is there any indication that scaling this hypothetical barrier with recombinant DNA methodology would have the consequences Sinsheimer predicts. But neither is there convincing evidence to the contrary. Our ignorance on this matter is but one aspect of the dilemma that obscures the search for wisdom.

To head off the hypothetical evolutionary consequences, Sinsheimer proposes that we should drastically curtail recombinant DNA research by relegating much of it to a few Federally supervised, impregnable laboratory facilities. He allows that, in time, we may discover the means to carry on this research "without risk" and then such work could return to nationwide institutional laboratories. Others, emboldened by Sinsheimer's stand, express metaphysical or religious concerns. Fearing the contents of this "Pandora's box" they shrink from the unknown and plead for a ban on all such experimentation throughout the world. Equally vociferous, but not as influential, are the advocates of unfettered research; they would leave responsibility in the hands of individual research workers and be content to rely on established methods for dealing with known dangerous organisms.

We, along with many others, have supported a different and middle-ground proposal. Our view is embodied in the "Guidelines for Research Involving Recombinant DNA Molecules" recently promulgated by the Director of the National Institutes of Health after nearly two years of intensive consultations. The guidelines aim to eliminate, or reduce to minimal levels, real and imagined risks associated with recombinant DNA research while permitting some experiments to proceed with caution. We believe this is the wise course, but it is important to explain why.

The so-called "moratorium" that started in the summer of 1974 and drew widespread attention to the potential biohazards of recombinant DNA research did not, as some believe, call for a ban on all recombinant DNA research. Only two types of experiments were of particular concern: the construction of drug resistant or toxigenic microorganisms that do not occur naturally and the introduction of all or part of the genomes of oncogenic viruses into bacterial cells. Each member of the committee which recommended deferral of these experiments agreed that the associated risks were likely to be viewed as clear-cut by most scientists in the field and that the anticipated benefits did not justify the potential hazards. The risks associated with other recombinant DNA experiments were less clear and, because of their speculative and controversial nature, caution and further consideration were urged. In the NIH guidelines, the experiments initially proscribed either remain proscribed or can be performed only under extremely stringent containment measures (of the sort recommended by Sinsheimer). Indeed, the number of experiments now proscribed by the NIH guidelines is substantially longer then was initially requested in the call for a moratorium.

What remains at issue, however, is the adequacy of the containment requirements mandated for permissible experiments. Sinsheimer and other critics regard the requirements as inadequate. On the other hand, we believe that the experimental and laboratory designs specified in the NIH guidelines afford the security needed to meet the perceived risks; they are in fact more stringent than most scientists estimate are needed for safety. The guidelines classify experiments according to the best available estimate of potential risk. Not all recombinant DNA experiments yield "new" organisms; recombination between the DNA's of organisms known to exchange genetic information in nature do not add uniquely man-made species to the biosphere. In these cases, the guidelines follow the general principle that the experiments are to be carried out under conditions generally used to handle the most hazardous parent of the recombinant. When DNA's from species not known to exchange genetic material in nature are recombined, more stringent and strictly defined containment is required, thereby increasing the physical isolation of the experimental material from both the experimenter and the outside world. There is documented experience on which to judge the efficacy of various physical barriers in preventing the escape of organisms. Moreover, in most such experiments it is mandatory to use genetically modified hosts and vectors that have been certified by NIH as unlikely either to propagate outside of rigorously defined laboratory environments or to transfer the recombined DNA to other cells. Thirty years of study of the genetic chemistry of E. coli strain K12 (an already enfeebled derivative of E. coli) provides confidence that with additional mutational modifications the capacity of these bacteria to escape and spread in the environment can be reduced to immeasurable levels. While it is important to investigate alternatives to E. coli K12, it is not at all certain that useful and safer organisms exist. Predictions about the existence of rare and fastidious organisms unable to exchange DNA with organisms inhabiting man or other living things are highly speculative.

The search for new knowledge always carries certain risks. Since the answers being sought are not known in advance, the extent of the hazards attendant upon discovery cannot be defined. Consequently, the assessment of risks, and the adequacy of the precautions designed to eliminate or minimize such risks, are matters of judgment based on objective, intuitive and value considerations. How much reliance should be placed on Sinsheimer's intuition versus that of other equally concerned individuals who assess the risks differently weighs heavily on our present deliberations. Were the risks Sinsheimer imagines more tangible, less remote, we would share his concerns and support his proposals. But, in our view, the risks he hypothesizes are imponderable and therefore the course he advocates is inappropriate and unwise; it is probably also unworkable. Relegating recombinant DNA research to special centers will cripple biological and medical research. This price is too high to pay for a risk that is so extraordinarily vague. Undeniably, more information is needed to assess fully the risks in this research. That information can be gained with minimal risk by expecting and insisting that scientists engaged in this work, wherever they are, adhere diligently to both the intent and letter of the NIH guidelines.

Sinsheimer and other responsible individuals who provide earnest arguments on the issues that confront us deserve our gratitude and respect. Their efforts will guide us along the path toward wisdom. But there are others, who misunderstand or have not assimilated the recent developments in biology. Of particular concern is the unwillingness of the latter to educate themselves regarding the substance of both the scientific and policy discussions that led to the decisions expressed in the guidelines. Thus far such individuals have distorted public discussion of a serious matter. They have attempted to discredit the urge to discover, enlighten and succeed and have attributed the enthusiasm of scientists in this field to obsessive ego gratification or the lure of Nobel awards. The uninformed advice of such men can only divert us from the wisdom we seek.

Citizens' Committee for the Conquest of Cancer
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EMERSON FOOTE
SOLOMON GARB, M.D.
KAY MANSOLILL

September 17, 1976

Senator Edward Kennedy
Subcommittee on Health
U.S. Senate
Washington, D.C. 20510

Dear Senator Kennedy,

I respectfully request that this letter be made part of the record of the Hearings on recombinant DNA research. This research is the most dangerous program ever undertaken by any person or group, and should be evaluated by the entire nation through the Congress, not by a small group of scientists with vested interests.

1. The key issue is not how recombinant DNA research should be done, but whether it should be done. A related issue is who should make the decision. Dr. Frederickson has assumed that he has the right and the authority to make the decision after seeking the advice of people whom he chooses to listen to. Many of us feel that he does not have any such right morally, and we would like clarification of his legal right to do this.

2. A glaring example of the inadequacy of the NIH guidelines is the section on inspection. NIH makes no realistic provision at all for outside inspection, but leaves all inspection for compliance with the guidelines in the hands of a committee at each university involved. To anyone, who like myself, has served on university committees for twenty years, it is ridiculous to expect any effective policing from such committees.

In other areas, concerned with public health and safety, there are legal requirements for inspection by government inspectors. These areas include restaurants, elevators, pharmaceutical manufacturers, meat packing companies, and even barber shops. Would we turn over inspection of a restaurant to a committee of the restaurant's employees? Would we turn over inspection of a meat packing firm to a committee of that firms employees? Hardly. Why then is Dr. Frederickson ready to turn over inspection of recombinant DNA research labs to colleagues in the same institution? Does he regard scientists as inherently more reliable than restaurant workers, meat packers, elevator operators, or barbers?

The significance of this omission of adequate and meaningful inspection extends beyond the question of inspection. It shows clearly that despite the voluminous and detailed published guidelines by NIH, there has not been the kind of mature, deliberate and unbiased consideration that a topic of this seriousness deserves. It also shows clearly that Dr. Frederickson and his advisors are not competent to make decisions of this nature. Thus, even the addition of a requirement for adequate outside inspection would not make the NIH position acceptable.

3. The hearings held by NIH were not as unbiased as Dr. Frederickson would have us believe. Those who testified in favor of recombinant DNA research had their travel expenses paid by their grants or their universities. Those who wished to testify against it would have been required to pay the travel expenses from their own pockets and couldn't afford to go. Therefore, the hearings were a distortion of true scientific sentiment.

4. Containment facilities are never absolute. They can reduce contamination but not eliminate it. The best containment facilities in the world, at Fort Detrich, failed several times, with infections and deaths resulting. Luckily, the failure did not involve organisms, like E. Coli that can replicate rapidly outside cells. Unfortunately, the recombinant DNA studies will involve E. Coli.

5. Dr. Frederickson claims that only a weakened strain of E. Coli would be used, and that the risk of its replication outside the laboratory is insignificant. We disagree. Dr. Frederickson may be 99.999% right. However, if one drop of culture containing the organisms splashes and gets outside the containment facility, some 100,000,000 bacteria may be involved. If 99.999% of them cannot survive, that still leaves 1,000 that can survive and replicate. If they contain viral genes, they could cause a deadly epidemic.

6. Some proponents of recombinant DNA research argue that genetic recombination takes place every day in nature and that doing it in the laboratory is not significantly more hazardous. That argument is a half-truth and completely misleading. The genetic recombination that takes place in nature is between closely related organisms, usually of the same species. The proposed laboratory studies, however, involve organisms of grossly dissimilar types. In the laboratory, scientists have created frog eggs that produce bee venom. When did that happen in nature?

7. Proponents of recombinant DNA research have contended that this research could lead to information that might unravel the mystery of cancer. These proponents have seldom if ever, had any responsibility for the medical care of patients with cancer. My personal opinion, based on years of cancer research, including responsibility for cancer patients, is that recombinant DNA research is far more likely to cause a cancer epidemic than it is to lead to clinically useful information about cancer.

In support of this opinion, I enclose a newspaper clipping dated May 28, 1976. Please note that scientists combined a harmless baboon virus with a mouse cancer virus that by itself is also harmless to other species. The hybrid virus, however, causes cancer in a wide variety of species, probably including man. Fortunately, it has not yet escaped from the laboratory.

8. I will take one example from the published NIH guidelines to show that despite their length and apparent detail, they are essentially worthless. It reveals that Dr. Frederickson either does not grasp the degree of hazard involved or is not telling us about it.

In explaining guideline VI, L on Page 27909 of the Federal Register, Dr. Frederickson discusses the concern of many commentators over the use of SV40 virus for recombinant studies. It is noteworthy that most of these commentators are generally in favor of recombinant DNA research and can be considered members of Dr. Frederickson's "team". On this particular point, however, even they felt that the risks were too great, and that recombinant DNA research using SV40 should be banned.

Dr. Frederickson overruled them and is permitting research with SV40 to proceed. His discussion and reasoning is based on his statement that there is no evidence that SV40, a monkey virus, can cause cancer in humans. That may be true of *unchanged* SV40. However, an altered SV40 could cause a disastrous cancer epidemic. Again, let us look at the enclosed May 28 newspaper clipping. A baboon virus harmless to man, and a mouse virus harmless to man, when combined, produce a virus that grows well in human cells, and that "scared" the scientists working with it. It is noteworthy that this newspaper report appeared *before* publication of the NIH guidelines. It is difficult to believe that Dr. Frederickson was unaware of it. How then can he claim that the lack of evidence of human harm from *unaltered* SV40 is reason to permit its continued use in experiments that alter it? This is especially disturbing since Dr. Frederickson's own allies and supporters have warned about Sv40.

I doubt if the Congress would allow a committee from the Pentagon to declare war, or allow a committee from the State Department to decide on foreign policy. Recombinant DNA research is a greater hazard than war, or errors in foreign policy. Therefore, decisions in this area should not be left to committees of scientists, loaded with those having vested interests in this area. Congress should investigate the area thoroughly, hearing from many experts including physicians, veterinarians, plant pathologists, disaster control experts, public health officials, nurses, and others who have experience in dealing with infectious disease. Also, groups concerned with the environment and natures' balance, such as Friends of the Earth, ought to be heard. Until such hearings are held, and until Congress decides on *whether* recombinant DNA research should proceed, all such research, however *funded*, should be stopped completely. Anything less might destroy mankind, and perhaps all higher forms of life on this planet.

Yours truly,

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